# McGill EPIB-671 Symposium - 2013

**Scientific Program, Friday, May 31**

<table>
<thead>
<tr>
<th>Time</th>
<th>Presenter</th>
<th>Title</th>
</tr>
</thead>
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<tr>
<td>13:00-13:15</td>
<td>Host</td>
<td>Introduction to the Event</td>
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<tr>
<td>13:30-13:45</td>
<td>Eileen Shaw</td>
<td>Reproductive Factors in HPV Infection and Cervical Cancer</td>
</tr>
<tr>
<td>13:45-14:00</td>
<td>Daniel Kiely</td>
<td>Cancer in Developing Countries: No Longer Off the Map</td>
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<tr>
<td>14:00-14:15</td>
<td>Fahad Al Rowais</td>
<td>Epidemiology of Bladder Cancer</td>
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<td>14:15-14:30</td>
<td>Khaled Adil</td>
<td>Finasteride in Prostate Cancer Prevention</td>
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<td>14:30-14:45</td>
<td>Hui Jun Wang</td>
<td>Gastric Carcinoma &amp; Helicobacter pylori Infection</td>
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<td>14:45-15:00</td>
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<td>Coffee/Ice Cream Break</td>
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<tr>
<td>15:00-15:15</td>
<td>Amal Al Odaini</td>
<td>Lung Cancer Screening</td>
</tr>
<tr>
<td>15:15-15:30</td>
<td>Anan Bamakhrama</td>
<td>Flavonoids and Cancer Prevention</td>
</tr>
<tr>
<td>15:30-15:45</td>
<td>Aurélie Garant</td>
<td>Non-ASA NSAIDS as Chemoprevention for Colorectal Cancer</td>
</tr>
<tr>
<td>15:45-16:00</td>
<td>Nicholas Winters</td>
<td>Air Pollution and Cancer</td>
</tr>
<tr>
<td>16:00-16:15</td>
<td>Livia Florianova</td>
<td>Exploring the Association Between HPV and Bladder Cancer</td>
</tr>
<tr>
<td>16:15-16:30</td>
<td>Dominique Boudreau</td>
<td>Colorectal Carcinoma and Ulcerative Colitis</td>
</tr>
</tbody>
</table>

16:30-17:00 Final remarks, take-home exam, and end of course: Have a Happy Summer!

Duration of presentations: 10 minutes; Q&A: 5 minutes
What is CEA?

Carcinoembryonic Antigen
M cG ill 1965
Normal & cancer cell expression
Immunoglobulin superfamily
Colorectal Cancer (CRC)
Why use tumour markers
Epidemiology 101: Screening & Diagnosis

Greenhalgh et al. BMJ 1997

Fletcher, R. Ann Int. Med. 1986

Figure 2. The positive predictive value of serum carcinoembryonic antigen levels for the detection of early (stages A and B) colorectal cancer according to the prevalence of disease (sensitivity = 40%, specificity = 90%).

Prevalence among people with symptoms?
The earlier the stage of CRC, the less likely a CEA assay is to detect it\(^8\).

For Stage I & II CRC: sensitivity 36% & specificity of 87\(^8\).

Stage III & IV: sensitivity 74%-83\%. 

---

Table 1. Some Conditions Associated with Elevated Plasma Levels of Carcinoembryonic Antigen Other Than Cancer

<table>
<thead>
<tr>
<th>Liver diseases</th>
<th>Alcoholic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic active</td>
<td>Primary biliary</td>
</tr>
<tr>
<td>Cryptogenic</td>
<td>Obstructive jaundice</td>
</tr>
<tr>
<td>Bowel diseases</td>
<td>Peptic ulcer</td>
</tr>
<tr>
<td></td>
<td>Pancreatitis</td>
</tr>
<tr>
<td></td>
<td>Diverticulitis</td>
</tr>
<tr>
<td></td>
<td>Inflammatory bowel disease</td>
</tr>
<tr>
<td>Other*</td>
<td>Smoking</td>
</tr>
<tr>
<td></td>
<td>Renal failure</td>
</tr>
<tr>
<td></td>
<td>Fibrocystic breast disease</td>
</tr>
</tbody>
</table>

*There are hundreds of case reports of elevations in various other, less common diseases.

Fletcher, R. Ann Int. Med. 1986
ASCO 2006 Update of Recommendations for the Use of Tumor Markers in Gastrointestinal Cancer


Position Paper

Clinical utility of biochemical markers in colorectal cancer: European Group on Tumour Markers (EGTM) guidelines

M.J. Duffy\textsuperscript{a,\,*}, A. van Dalen\textsuperscript{b}, C. Haglund\textsuperscript{c}, L. Hansson\textsuperscript{d}, R. Klapdor\textsuperscript{e}, R. Lamerz\textsuperscript{f}, O. Nilsson\textsuperscript{g}, C. Sturgeon\textsuperscript{h}, O. Topolcan\textsuperscript{i}

Clinical Chemistry 54:12
e11–e79 (2008)

National Academy of Clinical Biochemistry Laboratory Medicine
Practice Guidelines for Use of Tumor Markers in Testicular, Prostate, Colorectal, Breast, and Ovarian Cancers
Diagnosis: An Area of ambiguity.

**Consensus** that CEA as a marker for CRC in screening: **NOT RECOMMENDED**\(^5\)\(^-\)\(^7\)

- CEA for staging, post-operative, monitoring treatment to response **RECOMMENDED**


2.2.2. *Diagnostic aid*

As with screening, inadequate sensitivity severely limits the value of CEA for the diagnosis of early or low-stage CRC. In addition, as CEA can be elevated in the absence of malignancy, (e.g., in patients with benign liver disease and in subjects who smoke cigarettes [4,9]), specificity is also impaired. However, in patients with appropriate symptoms, a high serum CEA (e.g., > 5 times the upper limit of normal) is highly suggestive of an adenocarcinoma [10]. In this situation, further testing is necessary to confirm the presence of malignancy and locate the disease site. Although preoperative determinations of CEA are usually of little diagnostic value, the EGTG Panel recommends that the marker should be assayed at this point in patient management, i.e., in order to establish a baseline value and for assessing prognosis (see below).
How are we using CEA in MTL to Diagnose?

ER patients with CEA result:

N = 17,109 (M: 9,972, F: 7,136)

0.9% N = 157 (M: 72, F: 85)

Prior/ current malignancy?

Diagnosis of CRC in ER/Admission

0.09% (-) CRC N = 15

12% (+) CRC N = 33

(-) N = 124

(-) CRC N = 109

Patients seen in Emergency Room at Jewish General Hospital between March 1st and August 30th 2012 (6 months)

* confirmed pathologic diagnosis of colon/rectal cancer on colonoscopy/pathologic findings.

¶ no diagnosis of CRC after investigations performed in ER or upon current admission (imaging, colonoscopy)
Sensitivity and Specificity: Apples and Oranges
## Diagnosis of CRC (any stage)

<table>
<thead>
<tr>
<th>CEA status</th>
<th>(+) CRC</th>
<th>(-) CRC</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Normal 0-3μg/L)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(+) CEA &gt;3μg/L</td>
<td>10</td>
<td>35</td>
</tr>
<tr>
<td>(-) CEA 0-3μg/L</td>
<td>5</td>
<td>74</td>
</tr>
</tbody>
</table>

### RESULT:

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity:</td>
<td>0.67</td>
<td>(0.42-0.85)</td>
</tr>
<tr>
<td>Specificity:</td>
<td>0.68</td>
<td>(0.59-0.76)</td>
</tr>
<tr>
<td>Positive likelihood ratio:</td>
<td>2.08</td>
<td>(1.32-3.26)</td>
</tr>
<tr>
<td>Negative likelihood ratio:</td>
<td>0.49</td>
<td>(0.24-1.02)</td>
</tr>
<tr>
<td>Diagnostic odds ratio:</td>
<td>4.23</td>
<td>(1.34-13.31)</td>
</tr>
<tr>
<td>PPV</td>
<td>0.22</td>
<td></td>
</tr>
</tbody>
</table>

*Confidence intervals calculated using Wilson Score interval with p>0.05. Newcombe RG (1998). Interval estimation for the difference between independent proportions: Comparison of eleven methods. Statistics in Medicine, 17, 873-890.*
## Diagnosis of CRC (any stage)

<table>
<thead>
<tr>
<th>CEA status</th>
<th>(+) CRC</th>
<th>(-) CRC</th>
</tr>
</thead>
<tbody>
<tr>
<td>(+) CEA &gt;15μg/L</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>(-) CEA 0-15μg/L</td>
<td>11</td>
<td>104</td>
</tr>
</tbody>
</table>

### RESULT:

<table>
<thead>
<tr>
<th></th>
<th>CI:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity:</td>
<td>0.27 (0.11-0.52)</td>
</tr>
<tr>
<td>Specificity:</td>
<td>0.95 (0.90-0.98)</td>
</tr>
<tr>
<td>Positive likelihood ratio:</td>
<td>5.81 (1.75-19.28)</td>
</tr>
<tr>
<td>Negative likelihood ratio:</td>
<td>0.77 (0.57-1.05)</td>
</tr>
<tr>
<td>Diagnostic odds ratio:</td>
<td>7.56 (1.77-32.38)</td>
</tr>
<tr>
<td>PPV</td>
<td>0.44</td>
</tr>
</tbody>
</table>

*Confidence intervals calculated using Wilson Score interval with p>0.05. Newcombe RG (1998). Interval estimation for the difference between independent proportions: Comparison of eleven methods. Statistics in Medicine, 17, 873-890*
References


Reproductive Health Factors in HPV Infection and Cervical Cancer

EILEEN SHAW
M.SC. STUDENT
EPIB 671
MAY 31ST, 2013
Overview

Cervical cancer
- Epidemiology

Reproductive risk factors
- Contraceptives
- Vaginal health and hygiene

Conclusion
Human Papillomavirus

- Worldwide HPV prevalence in women – 11.4%
- Most commonly transmitted STI
- 90% of infections are cleared within 2 years
HPV and Cervical Cancer

3rd most common cancer in women, worldwide
- ~530,000 new cases diagnosed each year
- ~275,000 deaths
- 85% of new cases and 88% of deaths in developing countries
Factors Contributing to Cervical Cancer

- HPV is a necessary, but not sufficient cause of cervical cancer
- Established co-factors:
  - Tobacco smoking
  - Parity
  - Oral contraceptive use
  - Co-infection with HIV
- Co-factors can act in two ways:
  - Increasing the risk of acquisition or duration of HPV infection
  - Increasing the risk of progression from HPV infection to cervical cancer
Oral Contraceptives (OCs)

- Increased risk of cervical cancer with increased duration of use\(^2\)
- Cervical cancer risk decreases after cessation of OC use\(^2\)
  - Returns to that of never-users after 10 years
Oral Contraceptives (OCs)

Potential mechanisms:
- Decreased cellular immunity in clearing HPV
- Progression to cervical cancer via HPV gene expression and cell proliferation

Prevalence of HPV infection not increased
- IARC HPV Prevalence Surveys
Intrauterine Device (IUD)

- Protective role for IUDs by up to one half the risk
  - Low level immune response to fight cancer cells
  - Insertion/removal can remove some precancerous lesions
- Use of IUDs not found to affect HPV infection
Condoms

- Findings from meta-analysis show that condoms may not prevent HPV infection but can protect against genital warts, CIN and cervical cancer.

- Have been shown to promote regression of CIN and clearance of HPV in an RCT.
Other Contraceptive Methods

- **Spermicide**
  - Nonoxynol-9 increases susceptibility to HPV infection\(^7\)
  - Carrageenan shown to prevent HPV infection\(^8\)

- **Diaphragm**
  - No difference in HPV incidence or clearance\(^9\) with diaphragm plus lubricant gel\(^9\)

- **Tubal Ligation**
  - Some evidence of protective effect\(^10\)
  - Potential for secondary prevention
Inflammation

- Inflammation of the vagina/cervix can be due to:
  - Bacterial vaginosis (BV)
  - Yeast infection
  - Trichomonas infection
  - Other STIs

Role of inflammation in cervical cancer

- Evidence to suggest increased risk of CIN with Chlamydia and HSV-2 infection\textsuperscript{11, 12}
- Association between inflammation by BV and high grade lesions\textsuperscript{13}
Vaginal Hygiene

- Douching has been shown to increase risk of STIs
  - In HIV-positive women, douching found to be associated with HPV infection\textsuperscript{14}
  - Other studies show douching is associated with cervical lesions and possibly carcinogenesis\textsuperscript{15,16}

\begin{table}
\centering
\caption{Odds ratios (ORs) for cervical carcinoma in a metropolitan Utah study population, by douching frequency, 1984\textendash1987.}
\begin{tabular}{|c|c|c|c|}
\hline
Douching frequency & No. of cases & No. of controls & Crude OR & Adjusted* OR \\
& (\%) & (\%) & & \\
\hline
<10 times/lifetime & 64 (24) & 182 (45) & 1.0 & 1.0 \\
\hline
<1 time/month & 61 (23) & 102 (25) & 1.7 & 1.0 \textsuperscript{†} \\
\hline
1\textendash2 times/month & 81 (30) & 78 (19) & 3.0 & 1.2 \textsuperscript{†} \\
\hline
3\textendash4 times/month & 27 (10) & 32 (8) & 2.4 & 1.1 \textsuperscript{†} \\
\hline
>4 times/month & 33 (12) & 14 (3) & 6.7 & 4.7 \textsuperscript{†} \\
\hline
\end{tabular}
\textsuperscript{* Adjusted in a logistic regression model for age at interview, lifetime number of sex partners, cigarette smoking (in pack-years), religious activity, and educational level.}
\textsuperscript{†} 95\% confidence interval.
\end{table}
## Conclusion

<table>
<thead>
<tr>
<th>Factor</th>
<th>Role in HPV infection/cervical lesions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral Contraceptives</td>
<td>Increased risk of cervical cancer, but not associated with HPV prevalence</td>
</tr>
<tr>
<td>Intrauterine Device</td>
<td>Protective role for IUDs for cervical cancer, but does not affect the likelihood of HPV infection</td>
</tr>
<tr>
<td>Condoms</td>
<td>Reduced risk of CIN and invasive cervical cancer, inconsistent evidence in reducing HPV infection</td>
</tr>
<tr>
<td>Spermicide</td>
<td>N9 associated with increased HPV infection while carrageenan has been shown to prevent HPV infection</td>
</tr>
<tr>
<td>Diaphragm</td>
<td>No difference in HPV incidence or clearance</td>
</tr>
<tr>
<td>Tubal Ligation</td>
<td>Limited evidence- some showing a protective role in risk of cervical cancer</td>
</tr>
<tr>
<td>Inflammation</td>
<td>Limited evidence- most show increased risk of HPV carcinogenesis with cervical inflammation</td>
</tr>
<tr>
<td>Vaginal Hygiene</td>
<td>Douching associated with increased HPV infection (HIV positive women) and carcinogenesis</td>
</tr>
</tbody>
</table>
References


Cancer in developing countries: no longer off the map

Dan Kiely MDCM FRCSC
Large numbers, high case fatality, little spending

• 2/3 of 7.6 million deaths every year from cancer occur in low-income and middle income countries (1,2)

• Case fatality rates: 76% in low income countries; 46% in countries such as Canada (3,4)

• 5/80 cancer gap (1,3,5):

• < 5% of global health spending on cancer is low & middle income countries

• 80% of the global cancer burden is in low & middle income countries
Cancer case-fatality rates by country income and site. The case-fatality rate is the ratio of cancer mortality over the incidence.

Ginsburg O M et al. CMAJ 2012;184:1699-1704
Projected deaths by cause and country income: 2004, 2015, 2030. “Other noncommunicable diseases” include diabetes, chronic respiratory disease and mental illness.

Ginsburg O M et al. CMAJ 2012;184:1699-1704
SYNERGY and MULTIPLICATIONS

- Multiplications – of impacts on the family (particularly on children of mothers with cancer) (1)

Schematic Models of population health:

Model 1
Population Health = d1e1 + d2e2 + d2e3 + ...... 
\[ d = \text{disease} \]
\[ e = \text{expenditure} \]

Model 2
Population Health = d1e1*d2e2*d3e3.....

Model 3
Population health = Model 1 + Model 2
DIVISIONS

Division – “cancer thrives on the extraordinary force of divisions within society” (1)

“First and foremost is the acknowledgement to do something urgently – what (Martin Luther) King called “the fierce urgency of now”.(2)

A thought provoking modification (with at least some truth to it):
HRA →SEX→HPV→CIN

“Palliation to relieve pain and reduce suffering is a human right”(3)
Logistics, challenges

- Cancer registries – only 21% of the world’s population
- Radiation oncology
- Pathology
- Epidemiology
- Surgical capacity
- Medications
- Palliative care
Lessons from care of patients with HIV changed the world’s view of what is possible

• “Complex and (at least initially) expensive treatment became possible when accompanied by innovative treatment models and new investments” (1)

• “Neither care nor prevention can be neglected” (1)

• Prices are not fixed

• The impact of community health workers (1)

In practice: lessons from Rwanda

<table>
<thead>
<tr>
<th></th>
<th>Total reduction (2000-2011)</th>
<th>Global rank in annual rate of reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>AIDS deaths/100 000</td>
<td>78.4%</td>
<td>1</td>
</tr>
<tr>
<td>Deaths/1000 live births</td>
<td>70.4%</td>
<td>1</td>
</tr>
<tr>
<td>Maternal mortality ratio/100 000 live births</td>
<td>59.5%</td>
<td>6</td>
</tr>
<tr>
<td>HIV incidence/ 100 000</td>
<td>57.5%</td>
<td>8</td>
</tr>
</tbody>
</table>

“If you give Rwanda money to save the life of the oldest person in Rwanda today, we will make sure that the infant born tonight benefits too.”
-Agnes Binagwaho, Rwanda’s Minister of Health

In practice: Rolling out the HPV vaccine

- 275,000 women die from cervical cancer every year
- 88% live in developing countries
- “In 2011, Rwanda’s HPV vaccination programme achieved 93.23% coverage after the first three-dose course of vaccination among girls in grade six.” (1)

In Practice – GAVI (Global Alliance for Vaccines and Immunizations)

“Thanks to the GAVI Alliance, the poorest countries will now have access to a sustainable supply of HPV vaccines for as low as US$ 4.50 per dose. The same vaccines can cost more than $100 in developed countries and the previous lowest public sector price was $13 per dose.”

“First eight countries:
GAVI will begin support for HPV vaccines in Kenya as early as this month followed by Ghana, Lao PDR, Madagascar, Malawi, Niger, Sierra Leone and the United Republic of Tanzania.”

“Despite important success with the programme – patients have received treatments safely and with good outcomes – the reach of these pilot initiatives is dwarfed by the burden of disease.”

Knaul FM, Frenk J, Shulman LN:


A Challenge from Dr. Paul Farmer.

Could other hospitals develop this kind of partnership?
Ever hospital in America has a pathology department and a chemo program. You don’t need them all to do it, but the academic medical centers should be doing this.”

“It seemed as though they could not believe I was the one standing with them. I cannot explain the joy I felt....
APPENDIX – references and notes

• Slide 2


Slide 5 – Synergies and Multiplications

• Slide 6 - Divisions


• Slide 7 – Logistics, Challenges

• Cancer registries – only 21% of the world’s population is included (1)

• Radiation oncology – “massive undersupply” (1)

• Pathology – critical to cancer care - initiatives(5,6); local capacity building & partnerships (4)

• Epidemiology – debate as to role in advocacy (2); Beaglehole R et al – Public health at crossroads

• Surgical capacity - “Public health specialists now recognize that some surgical treatments not only prevent death and disability, but can be provided cost-effectively with low technology” (3)

• Medications – “Despite the fact that most essential drugs are off-patent and 22 are on the WHO Essential Medicines List, the availability of chemotherapy is limited” (1)

• Palliative care – “each year sub-Saharan Africa consumes barely enough medicinal opioids for

85 000 patients, yet records 1.3 million deaths in pain” (4, 8)


8) Knaul KM et al. Seizing the opportunity to close the cancer divide. The Lancet. Published online Feb 4, 2013. http://dx.doi.org/10.1016/S0140-6736(13)60176-2
November 2009 – “the Dana-Farber Cancer Institute, Harvard Medical School, and Harvard School of Public Health convened the Global Task Force on Expanded Access to Cancer Care and Control in Developing Countries (GTF.CCC)....The mandate of GTF.CCC is to design and implement global and regional initiatives for the financing and procurement of affordable cancer drugs, vaccines, and services, and through local partners, to develop and apply innovative service delivery models that can be monitored and evaluated to provide key evidence for expansion of cancer care and control in countries of low and middle income.”

EPIDEMIOLOGY & RISK FACTORS OF BLADDER CANCER

Fahad AL-Rowais
R1 Radiation Oncology
Epidemiology

- Bladder cancer is the most common malignancy involving the urinary system.

- Urinary bladder cancer ranks eleventh in worldwide cancer incidence and the seventh among males.
Estimated age-standardised incidence and mortality rates: both sexes

Estimated age-standardised incidence and mortality rates: men
Fig. 1 Age standardized incidence rates per 100,000 for UBC in males (a) and females (b)
Epidemiology

- Urothelial (transitional cell) carcinoma is the predominant histologic type in the United States and Western Europe, where it accounts for approximately 90% of bladder cancers.

- In other areas of the world, such as the Middle East, nonurothelial histologies are more frequent, at least in part to the prevalence of schistosomiasis.
In the United States, white males have the highest risk with roughly twice the incidence seen in African-American:
# 1. Incidence and Mortality by Cancer Type

Table 1.1

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>New Cases</th>
<th>Cases per 100,000</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total*</td>
<td>M</td>
</tr>
<tr>
<td><strong>All Cancers</strong></td>
<td>186,400</td>
<td>97,600</td>
</tr>
<tr>
<td>Prostate</td>
<td>26,500</td>
<td>26,500</td>
</tr>
<tr>
<td>Lung</td>
<td>25,600</td>
<td>13,300</td>
</tr>
<tr>
<td>Colorectal(^{1})</td>
<td>23,300</td>
<td>13,000</td>
</tr>
<tr>
<td>Breast</td>
<td>22,900</td>
<td>200</td>
</tr>
<tr>
<td>Non-Hodgkin Lymphoma</td>
<td>7,800</td>
<td>4,300</td>
</tr>
<tr>
<td>Bladder(^{2})</td>
<td>7,800</td>
<td>5,800</td>
</tr>
<tr>
<td>Melanoma</td>
<td>5,800</td>
<td>3,100</td>
</tr>
<tr>
<td>Kidney</td>
<td>5,600</td>
<td>3,500</td>
</tr>
<tr>
<td>Leukemia</td>
<td>5,600</td>
<td>3,200</td>
</tr>
<tr>
<td>Thyroid</td>
<td>5,600</td>
<td>1,250</td>
</tr>
<tr>
<td>Body of Uterus</td>
<td>5,300</td>
<td>—</td>
</tr>
<tr>
<td>Pancreas</td>
<td>4,600</td>
<td>2,200</td>
</tr>
<tr>
<td>Oral</td>
<td>4,000</td>
<td>2,700</td>
</tr>
<tr>
<td>Stomach</td>
<td>3,300</td>
<td>2,100</td>
</tr>
<tr>
<td>Brain</td>
<td>2,800</td>
<td>1,600</td>
</tr>
<tr>
<td>Ovary</td>
<td>2,600</td>
<td>—</td>
</tr>
<tr>
<td>Multiple Myeloma</td>
<td>2,400</td>
<td>1,350</td>
</tr>
<tr>
<td>Liver</td>
<td>2,000</td>
<td>1,500</td>
</tr>
<tr>
<td>Esophagus</td>
<td>1,850</td>
<td>1,400</td>
</tr>
<tr>
<td>Cervix</td>
<td>1,350</td>
<td>—</td>
</tr>
<tr>
<td>Larynx</td>
<td>1,050</td>
<td>860</td>
</tr>
<tr>
<td>Hodgkin Lymphoma</td>
<td>940</td>
<td>510</td>
</tr>
<tr>
<td>Testis</td>
<td>940</td>
<td>940</td>
</tr>
<tr>
<td>All Other Cancers</td>
<td>16,700</td>
<td>8,400</td>
</tr>
<tr>
<td>Non-Melanoma Skin</td>
<td>81,300</td>
<td>44,800</td>
</tr>
</tbody>
</table>

— Not applicable.

* Column totals may not sum to row totals due to rounding.

\(^{1}\) Definition for this cancer has changed; see Table A2.

\(^{2}\) Ontario does not currently report in situ bladder cases.

**Note:** "All Cancers" excludes the estimated new cases of non-melanoma skin cancer (basal and squamous).

**Analysis by:** Chronic Disease Surveillance and Monitoring Division, CCDCPC, Public Health Agency of Canada.

**Data source:** Canadian Cancer Registry database at Statistics Canada.
Risk Factors

- Environmental exposures account for most cases of bladder cancer.
- The surface epithelium (urothelium) that lines the mucosal surfaces of the entire urinary tract is exposed to potential carcinogens:
  - Excreted in urine
  - Activated in from precursors in the urine by hydrolyzing enzymes
Smoking

- The most important factor contributing to the overall incidence of urothelial cancer
- There are over 60 known carcinogens and reactive oxygen species present:
  - 4-aminobiphenyl (4-ABP),
  - Polycyclic aromatic hydrocarbons,
  - N-nitroso compounds and
  - Unsaturated aldehydes
Table 4. Relative Risks of Incident Bladder Cancer for Current Smokers Relative to Never Smokers in Previously Published Studies From US Prospective Cohorts

<table>
<thead>
<tr>
<th>Source</th>
<th>Cohort</th>
<th>Sex</th>
<th>Years</th>
<th>Mean Age</th>
<th>Never Smokers in Cohort</th>
<th>Cases in Never Smokers</th>
<th>Current Smokers in Cohort</th>
<th>Cases in Current Smokers</th>
<th>Percentage of Current Smokers Who Smoked ≥1 Pack of Cigarettes/d (Actual Cut Point Used in Each Cohort)</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alberg et al, 2007</td>
<td>Washington County, Maryland</td>
<td>Both</td>
<td>1963-1978</td>
<td>47</td>
<td>11,722 (26)</td>
<td>20 (22)</td>
<td>20,037 (44)</td>
<td>48 (52)</td>
<td>29 (&gt;20 cigarettes/d)</td>
<td>2.7 (1.6-4.7)</td>
</tr>
<tr>
<td>Chyou et al, 1993</td>
<td>Japanese men in Hawaii</td>
<td>Men</td>
<td>1965-1991</td>
<td>54</td>
<td>2,410 (30)</td>
<td>17 (18)</td>
<td>3,495 (44)</td>
<td>60 (63)</td>
<td>77 (≥20 cigarettes/d)</td>
<td>2.86 (1.67-4.91)</td>
</tr>
<tr>
<td>Mills et al, 1991</td>
<td>Seventh Day Adventists</td>
<td>Both</td>
<td>1976-1982</td>
<td>54</td>
<td>26,069 (76)</td>
<td>25 (52)</td>
<td>1,129 (3)</td>
<td>4 (8)</td>
<td>32 (≥25 cigarettes/d)</td>
<td>5.67 (1.73-18.61)</td>
</tr>
<tr>
<td>Alberg et al, 2007</td>
<td>Washington County, Maryland</td>
<td>Both</td>
<td>1975-1994</td>
<td>48</td>
<td>15,249 (32)</td>
<td>40 (23)</td>
<td>17,006 (35)</td>
<td>67 (39)</td>
<td>31 (&gt;20 cigarettes/d)</td>
<td>2.6 (1.7-3.9)</td>
</tr>
<tr>
<td>Tripathi et al, 2002</td>
<td>Iowa Women’s Health Study</td>
<td>Women</td>
<td>1986-1998</td>
<td>62</td>
<td>24,723 (66)</td>
<td>42 (38)</td>
<td>5,619 (15)</td>
<td>45 (41)</td>
<td>16 (&gt;20 cigarettes/d)</td>
<td>4.23 (2.76-6.70)</td>
</tr>
<tr>
<td>Michaud et al, 2001</td>
<td>Health Professionals Follow-up Study</td>
<td>Men</td>
<td>1986-1998</td>
<td>53</td>
<td>24,035 (49)</td>
<td>70 (23)</td>
<td>4,648 (9)</td>
<td>44 (14)</td>
<td>33 (&gt;25 cigarettes/d)</td>
<td>2.81 (1.85-4.27)</td>
</tr>
<tr>
<td>Cantwell et al, 2006</td>
<td>Breast Cancer Detection Demonstration Project Follow-up Study</td>
<td>Women</td>
<td>1987-2000</td>
<td>55</td>
<td>27,691 (57)</td>
<td>62 (44)</td>
<td>7,826 (16)</td>
<td>30 (21)</td>
<td>54 (&gt;20 cigarettes/d)</td>
<td>2.44 (1.56-3.80)</td>
</tr>
</tbody>
</table>

Summary estimate

| Both | 276 | 298 | 2.94 | (2.45-3.54) |

Abbreviations: CI, confidence interval; RR, relative risk.

Not all data were available in the original publication that examined the association of smoking and bladder cancer. For publications that lacked some of these variables, we identified other publications from the same cohort containing the desired information; references for these publications are marked where appropriate.

Alberg et al and Cantwell et al used Poisson regression models; Chyou et al, Mills et al, and Tripathi et al used Cox proportional hazards regression models; and Michaud et al used logistic regression.

Calculated from person-years in the original publication.

Cigarettes smoked per day for both former and current smokers combined.

Summary RR and 95% CI are from fixed-effects models. The P statistic for heterogeneity across studies was 0.0% and the Cochran Q test P value for between-study heterogeneity was 0.554.

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Smoking

- Although smoking cessation decreases the risk of bladder cancer, the available data suggest that the risk does not reach background levels even after 20 years or more.

- Smoking cessation also appears to decrease the recurrence rate for patients with non-muscle-invasive bladder cancer.
Occupational Carcinogens exposure

- Occupation has been identified as the second most important risk factor for bladder cancer, after smoking.

- The relationship between workplace exposure to various chemical carcinogens and an increased risk of urothelial cancer was first noted over a century ago.
Such exposures are thought to account for approximately 10 to 20 percent of bladder cancers.

Occupations that have been linked to an increased risk of bladder cancer include metal workers, painters, rubber industry workers, leather workers, textile and electrical workers.
Occupational Carcinogens exposure

- Exposure to aromatic amines (benzidine, 4-aminobiphenyl, b-naphthylamine, 4-chloro-ortho-toluidine) in:
  - Dyestuff manufacture,
  - Rubber and other industries
Fig. 1. Odds ratios for bladder cancer in European men by exposure to PAHs, BAP and diesel engine exhaust, using a job-exposure matrix.

Carcinogenic compounds have also been identified in hair dyes.

Hair dyes may contain a variety of chemical agents such as aromatic amines, some of which are carcinogens.

Changes in hair dye formulations and the widespread implementation of safety measures appear to have decreased this risk.
The available studies relate to exposures that occurred at different times over the last 30 years or more, during which period there were changes in both the types and quantities of products:

- 4-aminobiphenyl
- Benzidine
- Ortho-toluidie
4-aminobiphenyl

- 4-Aminobiphenyl was formerly used as a rubber oxidant.
- In addition, it may occur as a contaminant in some cosmetic colour additives, in hair dyes.
- There is sufficient evidence in humans for the carcinogenicity of 4-aminobiphenyl (bladder cancer).
- 4-Aminobiphenyl is carcinogenic to humans (Group 1).
4-aminobiphenyl

- Its production has been prohibited in the European Union since 1998, but it is still produced in some countries and supplied to countries where it is no longer produced.
Benzidine-based dyes were used primarily to colour textiles, leather, and paper products and also in the rubber, plastics, wood, soap and hair-dye.

Benzidine is carcinogenic to humans (Group 1).
Benzidine

- By the mid-1970s, most manufacturers started phasing-out the use of benzidine-based dyes and replacing them with other types of dyes.

- The manufacturing of benzidine is now prohibited in the EU and several other countries, e.g. Japan, the Republic of Korea, Canada and Switzerland.
Ortho-toluidine

- The aromatic amine ortho-toluidine is used in the production of dyes, pigments and rubber chemicals, and in laboratories to stain tissues.

- ortho-Toluidine causes cancer of the urinary bladder (group 1)
Multiple epidemiologic studies have established a link between high concentrations of arsenic in drinking water and the subsequent development of bladder cancer.

This relationship has been most clearly defined in areas of Chile and Taiwan, where subsequent removal of arsenic from drinking water sources led to a decline in the incidence of bladder cancer.
Chronic Cystitis

- Individuals with recurrent or chronic bladder infections and those who have an ongoing source of bladder inflammation have a higher risk of bladder cancer compared to the general population.

- In this setting, there is a substantially higher incidence of nonurothelial cancers, especially squamous cell carcinoma.
HPV

- Livia will take care !!
Iatrogenic

- Cyclophosphamide
- Analgesics
- Radiation
Patients treated with cyclophosphamide have up to a nine-fold increase in risk of developing bladder cancer, with a latency period that is generally less than 10 years.

Acrolein, a urinary metabolite of cyclophosphamide, is thought to be responsible for both hemorrhagic cystitis as well as bladder cancer.
The uroprotectant mesna inactivates urinary acrolein and can lower the subsequent risk of hemorrhagic cystitis as well as bladder cancer when used in conjunction with cyclophosphamide.
Phenacetin, an analgesic that was widely used until the third quarter of the 20th century, has been linked to an increased risk of TCC, particularly of the renal pelvis.

In the late 1980s, it was recognized as a carcinogen and removed from analgesic compounds in the United States and Europe, and largely replaced by acetaminophen, which does not increase the bladder cancer risk.
Several studies have shown an increased risk of bladder cancer following pelvic radiation for cervical, ovarian, prostate, and testicular cancers. However, this relationship has not been observed in all studies and the magnitude of the risk appears to be small.
Thank You
References

- International Agency for Research on Cancer
- Canadian Cancer Society
- Cancer Causes and Control 14: 907–914, 2003
- UpToDate, Topic 2957 Version 14.0
FINASTERIDE IN PROSTATE CANCER PREVENTION- AN ONGOING DEBATE THAT FINALLY HAVE REACHED AN END

Khaled Adil, MD
R1 Radiation Oncology
EPIDEMIOLOGY

- Prostate cancer incidence is 899,000 new cases, 13.6% of the total cancers. That makes it the second most frequently diagnosed cancer in men. Almost 75% of these cases diagnosed in the developed world.
- 258,000 deaths in 2008 have been reported secondary to prostate cancer which makes it the sixth leading cause of cancer related death in men (6.1% of the total).
- Aging population with expected 4 fold increase in men older than 65 by 2050.
TRENDS IN INCIDENCE AND MORTALITY FROM PROSTATE CANCER IN SELECTED COUNTRIES: AGE-STANDARDIZED RATE (W) PER 100,000

GLOBOCAN 2008 (IARC)
RISK FACTORS

¢ Age: In the United States, more than 70% of all patients diagnosed of prostate cancer are over 65 years of age.
¢ Ethnicity: one of the highest rates of prostate cancer in the world (275.3 per 100,000 men) is found in African Americans. That incidence is nearly 60% higher than among whites (172.9 per 100,000).
Family history: increased risk if one or more 1st degree relatives are affected. Also, it tends to be diagnosed at a younger age.

Other risk factors include: diet and obesity and most importantly hormones.
DEFINITION - AQUILINA ET AL, JNCI SEPT 1996

- “Chemoprevention refers to prevention of cancer or reduction of risk in susceptible individuals by administration of natural or synthetic drugs with little or no toxicity that suppress, delay, or reverse carcinogenesis”

- “Its most effective in the early stages of tumor development when reversibility is feasible”
GOOD CANDIDATE FOR CHEMOPREVENTION

- Long latency period – 10 years
- Hormone sensitive: androgen dependency: men with 5AR and deficiency and castrated don’t develop prostate cancer. Hormonal manipulation has side effects limit its use clinically
- Availability of clinical trials biomarkers: PSA and PIN-HG
HISTORY OF CASTRATION

- Normans invasion in the middle ages.
- Kingdom of Georgia
- Slave trade by the Arabs in the 10th century
- Convicted sex offenders in Czech republic
- Music and religion
FINASTERIDE

- Mechanism of action: type 2-5 AR inhibitor
- Why did they choose it?
- Uses: in BPH also reduces serum level of PSA by 50 %
- Dutasteride
**Table 2. Prostate cancer chemoprevention and chemoactive target population**

<table>
<thead>
<tr>
<th>Target population</th>
<th>Major advantage</th>
<th>Major disadvantage</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Chemoprevention</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1) General population</td>
<td>Findings directly applicable to general population</td>
<td>Requires large number of subjects</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Requires long study period</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Expensive</td>
</tr>
<tr>
<td></td>
<td></td>
<td>May require biopsy at end of study to establish status</td>
</tr>
<tr>
<td>2) High-risk groups (e.g., strong family history of prostate cancer)</td>
<td>Findings directly applicable to the high-risk group studied</td>
<td>Findings may not be applicable to general population</td>
</tr>
<tr>
<td>3) Prostatic intraepithelial neoplasia</td>
<td>Greatly decreases required sample size, study time, and expense</td>
<td>Possibility of coexisting cancer may be decreased by requiring second biopsy before treatment randomization</td>
</tr>
<tr>
<td></td>
<td>Easily identified on subsequent biopsies</td>
<td>Findings may not be applicable to general population</td>
</tr>
<tr>
<td><strong>Chemoactive</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1) Cancer on biopsy (treated during 3- to 12-wk period before radical prostatectomy)</td>
<td>Ability to evaluate whole-mounted pathology specimen</td>
<td>Only able to evaluate short-term effects of the chemopreventive agent</td>
</tr>
<tr>
<td>2) Cancer on biopsy treated by watchful waiting</td>
<td>Results would evaluate long-term effects of the chemopreventive agent on the cancer</td>
<td>Would require subsequent biopsies</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Findings may not be applicable to general population</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Findings may be confounded by the heterogeneity of prostate cancer</td>
</tr>
<tr>
<td>Study</td>
<td>Patients (n)</td>
<td>Age (years)</td>
</tr>
<tr>
<td>---------------</td>
<td>--------------</td>
<td>-------------</td>
</tr>
<tr>
<td>PCPT</td>
<td>18,883</td>
<td>&gt;55</td>
</tr>
<tr>
<td>REDUCE</td>
<td>8,231</td>
<td>55–75</td>
</tr>
<tr>
<td>SELECT</td>
<td>35,533</td>
<td>&gt;50</td>
</tr>
</tbody>
</table>

VIOLETTE ET AL, JABFM FEB 2012
PROSTATE CANCER PREVENTION TRIAL, NEJM JULY 2003

❖ Randomized, double-blind, placebo-controlled trial in which the effect of finasteride was investigated.
❖ Sample size: between 1993 and 1996, 18,882 men were recruited.
❖ Eligibility criteria: males 55 years of age or older with normal DRE and PSA less than 3 ng/mL; these men were stratified within each study arm according to age, race, and history of first-degree relative with prostate cancer.
Intervention: 5 mg of finasteride or placebo per day for 7 years proceeded by a 3-month enrollment period during which all participants received placebo before treatment randomization. Finally, around 9500 men were randomized in each arm. Over the study period, subjects were monitored for compliance and were screened annually with PSA and DRE. Subjects with an elevated PSA or suspicious DRE were referred for biopsy.

Primary end point: the prevalence of prostate cancer during the study. After 7 years of treatment, all survivors will underwent a sextant biopsy to ascertain the prevalence of prostate cancer.
Table 5. Gleason Scores for Prostate Cancers Detected.

<table>
<thead>
<tr>
<th>Gleason Score</th>
<th>All Cancers</th>
<th>Cancers Diagnosed in Biopsies Performed for Cause*</th>
<th>Cancers Diagnosed in End-of-Study Biopsies†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Finasteride Group (N=757)</td>
<td>Placebo Group (N=1068)</td>
<td>Finasteride Group (N=393)</td>
</tr>
<tr>
<td>2</td>
<td>4 (0.5)</td>
<td>9 (0.8)</td>
<td>3 (0.8)</td>
</tr>
<tr>
<td>3</td>
<td>1 (0.1)</td>
<td>8 (0.7)</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>15 (2.0)</td>
<td>38 (3.6)</td>
<td>7 (1.8)</td>
</tr>
<tr>
<td>5</td>
<td>69 (9.1)</td>
<td>118 (11.0)</td>
<td>38 (9.7)</td>
</tr>
<tr>
<td>6</td>
<td>388 (51.3)</td>
<td>658 (61.6)</td>
<td>157 (39.9)</td>
</tr>
<tr>
<td>7</td>
<td>190 (25.1)</td>
<td>184 (17.2)</td>
<td>118 (30.0)</td>
</tr>
<tr>
<td>8</td>
<td>45 (5.9)</td>
<td>25 (2.3)</td>
<td>32 (8.1)</td>
</tr>
<tr>
<td>9</td>
<td>36 (4.8)</td>
<td>24 (2.2)</td>
<td>29 (7.4)</td>
</tr>
<tr>
<td>10</td>
<td>9 (1.2)</td>
<td>4 (0.4)</td>
<td>9 (2.3)</td>
</tr>
<tr>
<td>7, 8, 9, or 10</td>
<td>280 (37.0)</td>
<td>237 (22.2)</td>
<td>188 (47.8)</td>
</tr>
</tbody>
</table>

* Not graded‡:

- All cancers: 803, 1147
- All men evaluated: 4368, 4692
- Cancers Diagnosed in Biopsies Performed for Cause: 1639, 1934
- Cancers Diagnosed in End-of-Study Biopsies: 3652, 3820

* Data include cancers diagnosed in biopsies performed for cause either during the study or at the end of the study and those diagnosed after interim procedures.
† Data exclude cancers diagnosed in biopsies performed for cause at the end of the study.
‡ Data are for cancers that were not graded either because they were too small to be graded (in 20 cases), because they were not reviewed centrally (in 103 cases), or for other reasons (in 2 cases).
RESULTS

- Prostate cancer was detected in 803 of the 4368 men in the finasteride group (18.4 percent) and 1147 of the 4692 men in the placebo group (24.4 percent), for a 24.8 percent relative risk reduction in prevalence over the seven-year period (95 percent confidence interval, 18.6 to 30.6 percent; P<0.001).
- Tumors of Gleason grade 7, 8, 9, or 10 were more common in the finasteride group 6.4 percent of the 4368 men compared to 5.1 percent of the 4692 men.
- Sexual side effects were observed more often in finasteride-treated men, on the other hand, urinary symptoms were more prevalent in placebo group.
DISCUSSION

- Finasteride causes shrinkage of the prostate this in turn will increase the sensitivity of DRE and rate of positive biopsy due to a more representative sampling.
- Finasteride induced changes caused grading bias may be the cause of high grade tumor in the finasteride group
- Tumors that develop in a low testosterone environment have higher grade
- Finasteride prevent only low grade tumors
- Over diagnoses in the study (24.4% in placebo vs lifetime of 16.7%)
LETS DEFINE THE INSIGNIFICANT TUMOR

The following characteristics proposed by Epstein in JAMA 1994 for an insignificant disease:

- Clinical factors (stage T1c and PSA density <0.15 ng/mL/g),
- Pathological: Tumor grade on biopsy (Gleason score ≤ 6, no Gleason pattern 4 or 5), and extent of tumor on biopsy [less than 3 cores with tumor (no core with >50% tumor) or <3 mm cancer present in only 1 core.]
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Gleason ≥6 (n = 389)</th>
<th>Finasteride</th>
<th>Placebo (n = 711)</th>
<th>Finasteride</th>
<th>Placebo (n = 191)</th>
<th>Finasteride</th>
<th>Placebo (n = 187)</th>
<th>Finasteride</th>
<th>Placebo (n = 91)</th>
<th>Finasteride</th>
<th>Placebo (n = 57)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (SD)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. cores positive (%)</td>
<td>1.40 (0.71)</td>
<td>1.0 (1-2)</td>
<td>1.55 (0.93)</td>
<td>1.0 (1-2)</td>
<td>1.99 (1.03)</td>
<td>2.0 (1-3)</td>
<td>2.36 (1.53)</td>
<td>2.36 (1-3)</td>
<td>2.59 (1.77)</td>
<td>2.98 (1.91)</td>
<td>3.0 (1.5)</td>
</tr>
<tr>
<td>Percent cores positive (%)</td>
<td>22.1 (11.3)</td>
<td>16.7 (12.3)</td>
<td>23.9 (16.4)</td>
<td>16.7 (12.3)</td>
<td>31.2 (16.4)</td>
<td>33.3 (14.3)</td>
<td>36.7 (20.3)</td>
<td>38.4 (16.7)</td>
<td>33.3 (16.7)</td>
<td>43.3 (16.7)</td>
<td>45.0 (20.5)</td>
</tr>
<tr>
<td>Greatest linear extent (mm)</td>
<td>1.76 (1.53)</td>
<td>1.30 (0.50-3.50)</td>
<td>1.95 (1.75-4.00)</td>
<td>1.30 (0.50-3.50)</td>
<td>4.13 (3.04)</td>
<td>4.20 (1.00-8.40)</td>
<td>4.56 (3.16)</td>
<td>4.00 (1.30-9.00)</td>
<td>4.97 (2.95)</td>
<td>5.45 (1.50-9.00)</td>
<td></td>
</tr>
<tr>
<td>Aggregate linear extent (mm)</td>
<td>2.31 (2.68)</td>
<td>1.40 (0.50-5.00)</td>
<td>2.72 (1.50-6.00)</td>
<td>1.60 (0.50-6.00)</td>
<td>6.66 (6.16)</td>
<td>4.50 (1.00-8.07)</td>
<td>8.18 (6.16)</td>
<td>5.50 (1.50-18.50)</td>
<td>9.61 (1.50-13.52)</td>
<td>12.37 (2.00-36.00)</td>
<td></td>
</tr>
<tr>
<td>Bilateral (%)</td>
<td>11.1</td>
<td>14.2</td>
<td>20.0</td>
<td>26.3</td>
<td>28.6</td>
<td>44.6</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Perineural invasion (%)</td>
<td>4.4</td>
<td>5.3</td>
<td>16.3</td>
<td>21.0</td>
<td>9.9</td>
<td>17.9</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median prostate volume (cm³)</td>
<td>23.8</td>
<td>32.7</td>
<td>25.1</td>
<td>33.5</td>
<td>23.8</td>
<td>38.8</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Median adjusted PSA (ng/mL)</td>
<td>1.80</td>
<td>2.00</td>
<td>3.40</td>
<td>3.70</td>
<td>4.80</td>
<td>4.60</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median PSA density (ng/mL/g)</td>
<td>0.07</td>
<td>0.06</td>
<td>0.13</td>
<td>0.09</td>
<td>0.19</td>
<td>0.12</td>
<td></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Medin insignificant biopsy cores</td>
<td>6</td>
<td>6</td>
<td>6</td>
<td>6</td>
<td>6</td>
<td>6</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insignificant cancer (criteria 1)</td>
<td>36.0</td>
<td>38.4</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insignificant cancer (criteria 2)</td>
<td>38.5</td>
<td>42.2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

* Comparison of number of cores positive significant for Gleason ≥6 (P = 0.024, Kruskal-Wallis test).
* Comparison of percent cores positive significant for Gleason 7 (P = 0.009, Kruskal-Wallis test).
The criteria of tumors diagnosed by biopsy (number and percent of positive cores, extent of tumor, bilaterality, and perineural invasion) point that finasteride-treated group had smaller and less aggressive tumors.

This difference reached statistical significance for number of cores positive in Gleason score ≤ 6 tumors, percent of positive cores for Gleason score 7 tumors, and percent of bilateral tumors in Gleason score ≥ 8 tumors despite smaller prostate in the experimental arm.
REGULATORY BODIES GUIDELINES

- ASCO and AUA 2008:
  - Men should be well-informed, asymptomatic with a PSA ≤3.0 ng/mL and engaged in regular screening to get the possible benefit from the use of a 5-ARI.
  - However, the use of 5-ARIs is not recommend in all men, there wasn't specific trigger to initiate further investigation.
FDA 2011: confirmed the 23% - 25% risk reduction of prostate cancer. But the concern regarding the risk of high grade disease as being estimated to be 1 in 150 to 200 men on the treatment leads to the disapproval of this indication.
REFERENCES

- International agency for research in cancer
- Epidemiology of prostate cancer, Crawford, Urology, December 2003
- The Influence of Finasteride on the Development of Prostate Cancer, Thompson et al, NEJM July 2003
- Chemoprevention of Prostate Cancer: Myths and Realities, Violette et al, JASFM Feb 2012
Gastric cancer & *Helicobacter pylori* infection
Gastric cancer epidemiology

- Leading cause of cancer deaths in the world until the 1980s
- One of the most common diagnosed cancer in the world, especially in some developing countries
- Approximately 21,600 patients are diagnosed annually in the United States, 10,990 are expected to die (Globocan database).
- 3rd in men and 4th in women fatal carcinoma worldwide
- The worldwide incidence of gastric cancer has declined rapidly over the recent few decades
- Refrigeration and diminish consuming salted and smoked food contribute to this decline
- Part of the decline may be due to the recognition of certain risk factors such as *H. pylori* and other dietary (fresh vegetables) and environmental risks
Global incidence of gastric cancer in men

Risk factors: environment

• Diet:
  Salt and salt-preserved food
  N-nitroso compounds (diet, tobacco smoking, endogenous)
  Fruits, vegetables, fiber intake reduce the risk

• Obesity
• Smoking
• *Helicobacter pylori* (*H. pylori*) infection
• Epstein-Barr virus
• Alcohol
• Socioeconomic status
• Gastric surgery: Billroth’s procedures
• Reproductive hormones
Risk factors: host factors

- Blood group: group A has increased risk in pernicious anemia and stomach cancer. It is possible that the observed associations are not due to the blood group antigens themselves, but to the effects of genes closely associated with them.
- Family predisposition:
  - clustering *H. pylori* infection in family
  - genetic predisposition for chronic atrophic gastritis
    - Hereditary diffuse gastric cancer, HNPCC
- Gastric ulcers
- Gastric polyps: low, 0.5-7% malignancy potential
- Pernicious anemia
- Hypertrophic gastropathy (Ménétrier’s disease)
- Immunodeficiency syndrome
Helicobacter pylori

• *H. Pylori* is Gram(-), micro-aerophilic bacterium, generally found in stomach and up GI tract
• Spiral-shaped, 3μm X 0.5μm diameter, has flagella at one end
• Found in 1982 by Dr. Barry Marshall and Dr. Robin Warren (Australia physician). In 1994, NIH consensus conference recognized *H. pylori* as a cause of gastric and duodenal ulcers. Later 1994, the International Agency for Research on Cancer (IARC) declared *H. pylori* to be a group I human carcinogen for gastric adenocarcinoma
• There is also evidence that *H. pylori* infection is a risk factor for gastric mucosa-associated lymphomas
Epidemiology of *H. pylori* infection

- Most widespread infection in the world, >50% of population are been infected
- Incidence: developing countries (about 70-75%) > developed countries (25%)
- Transmission route is not known yet, most likely person to person by oral-oral or fecal-oral, possibly also by water contamination
**H. Pylori features**

**Flagella**, allow the bacteria to be motile in viscous mucus

**Urease**, generates ammonia from endogenous urea‡ increase local PH

**Adhesins**, enhance their bacterial adherence to surface foveolar cells

**Toxins**, such as cytotoxin-associated gene A (CagA), involved in ulcer or cancer
Association between H. pylori infection and gastric carcinoma

- The **EUROGAST study** of 17 populations from 13 different countries (11 European countries, the United States, and Japan) found a **six-fold increased risk of gastric cancer in H. pylori-infected populations compared with uninfected populations**.

- A nested case-control study of Japanese Americans living in Hawaii, *H. pylori* sero-positivity was present in 94% of patients with gastric cancer compared with 76% of matched controls; the **odds ratio** was **6.0**.

- Two meta-analysis of cohort and case-control studies examining the relationship between *H. pylori* sero-positivity and gastric cancer found that **H. pylori infection was associated with a twofold increased risk for developing gastric adenocarcinoma**.

- One of the largest prospective studies addressing *H. pylori* and cancer risk included 1526 Japanese patients, 1246 had *H. pylori* infection, f/u with endoscopy & biopsy. During a mean f/u of 7.8 years, 36 patients developed gastric cancer (2.9%), all of whom were *H. pylori* infected. No uninfected patient developed cancer.
Disease evolution

*H. pylori* Infection

↓

Chronic gastritis

↓

Multiple mucosal atrophy

↓

Intestinal metaplasia

↓

Intraepithelial neoplasia

↓

Gastric cancer
Pathology

Gastric mucosal atrophy

↓

Acid secretion reduced‡ altered PH

↓

Gastric bacteria flora changed

↓

Anaerobic bacteria colonized

↓

Active reductase transform food nitrate‡ nitrite

↓

Nitrite reacting with amines, amides and urea‡ nitroso compounds (carcinogenic)
Possible mechanisms of Helicobacter pylori-induced gastric carcinogenesis

Indirect: Helicobacter pylori and chronic gastritis
Inflammation:
- Free radical production
- Decreased ascorbate
- Increased gastrin

Direct: Epithelial cell damage
- Cell proliferation
- Increased N-nitroso compounds
- Atrophic gastritis
  - Decreased acid secretion

Mutation:
- Low ulcer risk

Eradication of *H. pylori* infection

- As gene mutations are likely to develop at an early stage of gastritis demonstrated by some studies, eradication at an early stage of *H. pylori* infection is strongly recommended.
- Eradication *H. pylori* with antibiotics.
- The standard first-line therapy is a one week "triple therapy" consisting of:
  - Proton pump inhibitor
  - Clarithromycin and
  - Amoxicillin
Primary prevention: vaccination

• Extensive vaccine studies in mouse models have shown promising results.

• A vaccine against *H. pylori* infection is undergoing Phase I clinical, and has shown an antibody response against the bacterium. Its clinical usefulness requires further study.

• The vaccination plan and the groups who should receive vaccination are still to be determined, the vaccination will be useful in high prevalent countries.
<table>
<thead>
<tr>
<th>Risk factors</th>
<th>Risk for developing gastric cancer</th>
<th>Recommendation</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Helicobacter pylori (HP) infection</td>
<td>Odds ratio (OR): 2.3</td>
<td>High risk area - mass screening possible benefit</td>
<td>Huang 1998</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Low risk area - mass screening not cost-effective</td>
<td></td>
</tr>
<tr>
<td>1. HP without atrophic gastritis</td>
<td>1. Hazard ratio 7.13 (compared with no HP)</td>
<td>See above</td>
<td>Ohata 2004</td>
</tr>
<tr>
<td>2. HP with atrophic gastritis</td>
<td>2. Hazard ratio 14.5</td>
<td>HP eradication</td>
<td></td>
</tr>
<tr>
<td>3. Atrophic gastritis and extensive intestinal metaplasia</td>
<td>3. Hazard ratio 61.9</td>
<td>HP eradication</td>
<td></td>
</tr>
</tbody>
</table>
Summary

• *H. pylori* infection has been identified as group 1 human carcinogen for gastric adenocarcinoma

• Early eradication by antibiotics can reduce incidence of gastric cancer in *H. pylori* infected patients

• Mass screening may benefit for high prevalent countries or areas
References


11. Uptodate
Thank You!
Lung Cancer Screening

By: Amal A. AlOdaini, MD, M.Sc.
PGY-1 Anatomical Pathology
Introduction- Epidemiology

- The leading cause of cancer related death in males and females.

- In 2013, American cancer society predicts
  - 228,190 new cases.
  - 159,480 lung cancer associated death.
Lung Cancer Risk Factors

• **Smoking**
  ▫ The risk of a current smoker of a pack / day for 40 years is 20 X higher than the non smoker.

• **Radiation therapy**
  ▫ e.g. post radiation in breast cancer and HL patients.

• **Environmental toxins**
  ▫ Asbestos, radon.

• **Pulmonary fibrosis**
  ▫ 7X increase in the risk independent of smoking.
Clinically ...

- The majority of patients with lung cancer have already metastasis at time of diagnosis.

- As such, surgery is usually curative at early stage.
  - Stage IA/IB‡ 70% 5-year survival rate.
  - Stage IIA/IIB‡ 50% 5-year survival rate.
Screening of lung cancer would be effective because ..

- Its high morbidity and mortality.

- Significant prevalence (0.5 to 2.2 percent).

- Identified risk factors allowing targeted screening for high risk.

- A lengthy pre-clinical phase.

- Evidence that therapy is more effective in early stage disease.
The Ideal Screening Test

- High sensitivity
- High specificity
- Relative safety
- Acceptability
- Relative low cost
- Reduce mortality, improve quality of life

Out comes to be assessed

- Cancer detection rates
- Stage at detection
- Survival
- Overall mortality
- Disease-specific mortality
Methods for Lung Cancer Screening

- CXRs
- Sputum cytology
- Low dose CT (LDCT)
- Others
  - Automated sputum image cytometry
  - Autofluorescence bronchoscopy
  - Exhaled breath analysis
  - Blood tests- serum protein microarray for molecular markers.
Chest X-ray ± Sputum analysis

- There have been seven large scale controlled clinical trials; 6 RCTs and one non randomized.

- The majority compared more frequent screening vs. less screening.

- Randomized trials conducted in the 1970s and 1980s using screening sputum cytology and chest radiographs failed to detect a significant reduction in lung cancer mortality in the group offered more extensive screening.
PLCO Trial

- 1993-2001
- Included 154,901 individuals 55-74 year old.
- Baseline CXR and three year annual CXR. vs. standard care.
- Differs from previous:
  - First to compare intervention versus no intervention.
  - Equal men and women
  - Has a sub group which can be compared to NLST
ACCP Recommendations

• In patients at risk of developing lung cancer, screening with CXR once or at a regular intervals is not recommended (Grade 1A).

• In patients at risk for developing lung cancer, screening with sputum cytology at regular intervals is not recommended (Grade 2B).
Screening with LDCT

• Results are available from
  ▫ One large randomized trial, the National Lung Screening Trial (NLST).
  ▫ Several observational cohort studies

• Additional randomized trials are ongoing

• Systematic review at 2012, identified NLST as the only trail which demonstrate mortality reduction.
National Lung Screening Trial

- RCT conducted at 33 US medical centers.
  - 53,454 subjects (male/female), current and ex-smokers.
  - 55-74 years of age, 30 pack-years.
  - Compared annual LDCT vs. CXR for three years.
- Trial was stopped 2010 after interim analysis showing that over a median follow up of 6.5 years:
  - Incidence rate ratio of 1.13 (CI 95% 1.03-1.23)
  - Relative mortality reduction of 20% (CI 95% 3.8-26.7)
  - 7% reduction in all cause mortality (CI 95% 1.2-13.6).

<table>
<thead>
<tr>
<th>Study</th>
<th>Screen modality: no. participants</th>
<th>Noncalcified nodules (baseline)</th>
<th>Total no. of cancers detected</th>
<th>Surgical stage I</th>
<th>Deaths from lung cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>NLST [16]</td>
<td>CT: 26722 CXR: 26732</td>
<td>27.3** 9.2</td>
<td>1060 941</td>
<td>50% 30.7%</td>
<td>356 443</td>
</tr>
</tbody>
</table>
ACCP/ASCO/AATS/NCCN Recommendations

• For smoker and former smoker who are age 55-74 and who have smoked ≥ 30 pack a year or have quit within the past 15 years, LDCT should be offered, but only in setting that can deliver the comprehensive care as in the trail (Grade 2B).

• For individuals who have accumulated < 30 pack a year or < 55, > 74, individuals who quit smoking >15 years, and for individuals with sever comorbidity that can preclude treatment; screening should not be performed (Grade 2C).

ACCP-American College of Chest Physicians
ASCO-American Society of Clinical Oncology
AATS-American Association of Thoracic Surgery
NCCN-National Comprehensive Cancer Network
Potential Harms of Screening

• Detection of abnormalities that requires further evaluation, most of which are benign nodules.
  ▫ In NLST trial, among abnormal results (24.2 % of CT scans and 6.9 % of radiographs), 96 % were false positive, and 11 % of the positive results led to an invasive study.

• Complication of diagnostic procedure.

• Radiation exposure.

• Quality of life.
  ▫ Prolonged follow-up of nodules, may cause anxiety related to fear of having lung cancer.
RISK PREDICTION MODELS FOR SCREENING

- PLCO trial model
  - Age
  - Education
  - Body mass index
  - Family history
  - History of chronic lung disease
  - Smoking status

- Liverpool Lung Project (LLP) model
  - Smoking duration
  - History of pneumonia
  - History of cancer
  - Family history of lung cancer
  - Asbestos exposure
Summary

• Lung cancer is responsible for one third of cancer related death in males and one fourth in females.

• Out of different clinical modalities, LDCT proves to be the only promising screening tool with 20 % mortality reduction.

• There are some challenges for LDCT implementation.

• Further validation for the risk predicting models is needed in relation to NLST.

• Other screening modalities( molecular) are still under investigations.
References


Canadian Cancer Association

Up to date

Screening for Lung Cancer Diagnosis and Management of Lung Cancer, 3rd edition: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines, Chest


Thanks!
FLAVONOIDS AND CANCER PREVENTION
Flavonoids are a class of plant secondary metabolites with various health benefits.

One of the major benefits is cancer prevention.
WHERE CAN WE FIND IT?

Tea is a major dietary source of flavonoids of which the flavan-3-ols catechins are the most common in dry (green > black) tea leaves.

They are found also in fruits, vegetables, and wine.

<table>
<thead>
<tr>
<th>Subclass</th>
<th>Compound</th>
<th>Major food sources</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flavonols</td>
<td>Kaempferol, myricetin, quercetin</td>
<td>Onions, kale, broccoli, apples, cherries, fennel, sorrel, berries, tea</td>
</tr>
<tr>
<td>Flavones</td>
<td>Apigenin, luteolin</td>
<td>Celery, parsley, thyme, red pepper</td>
</tr>
<tr>
<td>Flavanones</td>
<td>Hesperidin, naringenin</td>
<td>Citrus, prunes</td>
</tr>
<tr>
<td>Flavan-3-ols</td>
<td>Catechins (C) and gallic esters of catechins (CG), epicatechins (EC), ECG, epigallocatechin (EGC), EGCG, teaflavins and gallic esters of teaflavins</td>
<td>Tea, apples, cocoa</td>
</tr>
<tr>
<td>Anthocyanidins</td>
<td>Cyanidin, delphinidin, malvidin, pelargonidin, peonidin, petunidin</td>
<td>Cherries, grapes</td>
</tr>
<tr>
<td>Isoflavones</td>
<td>Genistein, daidzein, glycitein, formononetin, biochanin A</td>
<td>Soya beans, legumes</td>
</tr>
</tbody>
</table>

*Data are from the USDA Database for the Flavonoid Content of Selected Foods, Release 3, 2011 (160) and Isoflavone Content of Selected Foods, 2008 (161), and USDA Database for the Flavonoid Content of Selected Foods, Release 2.1, 2007 (88).*
There is heterogeneity in the intake of flavonoids among populations residing in the United States, Europe, and Asia likely due to different agricultural, sociodemographics, and lifestyle factors.

In diet of U.S. adults, the flavonoid density is higher in women, and it approaches 190 mg/day.

In Europe, the flavonoid intake was higher in women, nonsmokers, and increased with level of education and physical activity.

Studies that estimated isoflavone intake in adults residing in Japan, China, Hong Kong, and Singapore found that 10% of the overall Asian population consumed 100 mg/d of isoflavones.

The combined intake of flavones in the United States is lower compared to that of populations residing in Europe. Moreover, the intake of isoflavones in U.S. women is considerably lower compared to that of women residing in Asia.

These differences in flavonoid intake may explain the higher susceptibility to certain types of cancers (e.g., breast cancer) in the United States compared to other geographical areas.
Interest in the anticarcinogenic effects of flavonoids has emerged from in vitro and in vivo experimental evidence indicating they interfere with cancer processes such as:
- proliferation
- inflammation
- angiogenesis
- invasion
- metastasis.

At the Molecular level:

Targets for flavonoids:
- mitogen-activated protein kinase (MAPK)
- protein kinase C (PKC)
- phosphatidylinositol 3-kinase (PI3K)
- β-catenin

Flavonoids also induce cell cycle arrest and apoptosis.
Oral Cancers

Case-control studies by Rossi.M in Italy

- A Network of Case-Control Studies
  Published 2010 in the Nutrition and Cancer Journal
  10,000 cases oral, and pharyngeal cancer
  16,000 controls

- Flavonoids and laryngeal cancer
  Conducted in Italy 1992 and 2000
  460 cases
  1088 controls

Showed inverse association between flavonoids and risk of cancer.

A double-blind intervention trial was conducted in patients with oral mucosa leukoplakia using a mixed tea product
59 patients were randomly divided into
- treated group (3 g mixed tea oral administration)
- control group (placebo and glycerin treatment).
6 month trial the size of oral lesion was decreased in 37.9% of the 29 treated patients and increased in 3.4 was decreased in 10.0% of the 30 control patients and increased in 6.7%
Gastrointestinal Cancers

Two case-control studies

1) Flavonoids and risk of squamous cell esophageal cancer
   Case-control study, published in the International Journal of Cancer
   Between 1992 and 1997 in Northern Italy
   304 cases with esophageal squamous-cell carcinoma
   743 controls
   The study suggests that flavonoids (citrus fruits) intake is inversely associated with esophageal cancer risk and may account, with vitamin C, for the protective effect of fruit.

2) In Italy, published 2010 by Bosetti and Rosato
   230 cases of gastric ca
   547 controls
   Reported that dietary proanthocyanidins correlated with reduced incidence of gastric cancer.

Cohort Study
   Data were collected in Hawaii and California in 1993-1996
   183,518 participants
   During 8 years of follow-up showed that The intake of kaempferol was inversely related to risk of pancreatic cancer
Colorectal Cancers

Three case-control studies & 1 Cohort study conducted in Japan

1) published 2011 by Budhathoki in the Journal of Gastroenterology
   816 cases of colorectal cancers
   815 controls
   reported inverse association

2) published 2009 in the British Journal of Cancer by Akhter
   721 cases
   697 controls
   the observed association was more prominent in women than in men

Lung cancer

Limited studies

In a prospective cohort study published 2008
2,590 middle-aged men
62 lung cases
Conclusion → high intake of flavonoids is associated with decreased risk of lung cancer
Prostate and Cancer

Two case control studies showed no association

1) Conducted in Scotland, published 2007
   - 433 cases of prostate cancer
   - 483 controls

2) Conducted in Italy, published 2006
   - 1,294 cases
   - 1,451 controls

BREAST CA

A strong protective effect of falvonoids on breast cancer was reported in different studies.
(At least 4 case control studies, 1 cohort study)
Major one was a case control study in New York, published in 2007
1,434 cases
1,440 controls
reported reduced risks of breast cancer

Published in 2011 in the American Journal of Epidemiology; a meta-analysis that examined the association between isoflavones intake and breast cancer risk in 14 prospective studies of breast cancer incidence, and 4 prospective studies of recurrence showed inverse association between breast cancer incidence among Asian women and isoflavones intake.
A major challenge in flavonoids and cancer research is that most of the epidemiological data originated from case-control studies that relied on retrospective acquisition of data through food frequency questionnaires, which can be biased due to errors in recall and personal prejudices. Although some cohort and randomized-controlled trials have proposed a cancer protective effect for certain flavonoids, the development of recommendations for humans has been hampered by the multitude of biological actions, and difficulties in assessing food composition and bioavailability.

Prospective studies with larger sample sizes are necessary to reduce bias and calibrate the effects of specific flavonoids and interactions on the cancer response.
Flavonoids are polyphenolic compounds that are distributed widely in the plant kingdom; they are especially abundant in tea, fruits and vegetables.

Flavonoids have many possible biological effects that may play a role in cancer prevention. Studies showed that flavonoids have protective effects against various types of tumors including oral and pharyngeal, gastric, pancreatic, colorectal, hepatic, prostate, ovarian, endometrial, breast, and lung cancers.
References


QUESTIONS !!

Thank you
Non-ASA NSAIDS as Chemoprevention for Colorectal Cancer

A. Garant
EPI B 671 Symposium
May 31, 2013
Introduction - Epidemiology

Source: GLOBOCAN Colorectal Cancer Fact Sheet, IARC 2008
Pathogenesis

Screening & Prevention

Current standards

- Screening for colorectal cancer should occur after risk stratification which determines the appropriate screening test and interval
- Fecal immunohistochemical test (FIT) every 1-2 years for average-risk individuals aged 50-75 years
- Follow-up of ANY positive fecal occult blood test (FOBT) with colonoscopy
- Use of FOBT is not appropriate when frank blood is present
- Colonoscopy every 10 years is an acceptable alternative to FOBT for screening
- Patients followed by colonoscopy do not require other screening modalities (ie. FOBT)

Source: http://www.cma.ca/clinicalresources/practiceguidelines
Table 55.2. Chemoprevention Clinical Trials of Nonsteroidal Anti-inflammatory Drugs and Adenomatous Colorectal Polyps

<table>
<thead>
<tr>
<th>Population</th>
<th>Drug (Dose), Duration</th>
<th>Phase</th>
<th>End Point</th>
<th>Outcome</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>SPORADIC RISK</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Previous adenomatous polyps</td>
<td>Sulindac (300 mg), 4 mo</td>
<td>2b</td>
<td>Polyp regression</td>
<td>Sulindac did not significantly decrease the number or size of polyps</td>
<td>24</td>
</tr>
<tr>
<td>Previous adenomatous polyps</td>
<td>Piroxicam (7.5 mg), 2 y</td>
<td>2b</td>
<td>Polyp regression</td>
<td>Colorectal mucosal PGE2 reduced in piroxicam-treated arm, unacceptable</td>
<td>25</td>
</tr>
<tr>
<td>Previous adenomatous polyps, healthy subjects</td>
<td>Aspirin (40, 81, 325, 650 mg qd), 1 day, 4 wk</td>
<td>1, 2a</td>
<td>Dose-biomarker</td>
<td>Aspirin dose of 81 mg daily sufficient to suppress colorectal mucosal</td>
<td>128-130</td>
</tr>
<tr>
<td>Prior colorectal cancer</td>
<td>Aspirin (325 mg qd), 3 y</td>
<td>2b</td>
<td>Polyp regression</td>
<td>Aspirin use associated with delayed development of adenomatous polyps</td>
<td>131</td>
</tr>
<tr>
<td>Previous adenomatous polyps</td>
<td>Aspirin (61 mg qd or 325 mg qd) and/or folate, 3 y</td>
<td>2b</td>
<td>Polyp regression</td>
<td>Low-dose aspirin reduced the recurrence of adenomatous polyps</td>
<td>132</td>
</tr>
<tr>
<td>Previous adenomatous polyps</td>
<td>Celecoxib</td>
<td>2b</td>
<td>Polyp regression</td>
<td>Celecoxib reduced the recurrence of adenomatous polyps, unacceptable</td>
<td>27</td>
</tr>
<tr>
<td>Previous adenomatous polyps</td>
<td>Celecoxib</td>
<td>2b</td>
<td>Polyp regression</td>
<td>Celecoxib reduced the recurrence of adenomatous polyps, unacceptable</td>
<td>26</td>
</tr>
<tr>
<td>Previous adenomatous polyps</td>
<td>Rofecoxib</td>
<td>2b</td>
<td>Polyp regression</td>
<td>Rofecoxib reduced the recurrence of adenomatous polyps, unacceptable</td>
<td>28</td>
</tr>
</tbody>
</table>

### Table 1. Chemopreventive Efficacy of Regular Use of Nonsteroidal Anti-inflammatory Drugs (NSAID)*

<table>
<thead>
<tr>
<th>Study, Year (Reference)</th>
<th>Participants, n</th>
<th>Quality Score</th>
<th>Population</th>
<th>Dose and Duration</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Effects on the incidence of CRC</strong>&lt;br&gt;Cohort studies (n = 3)&lt;br&gt;Nurses’ Health Study; Chan et al., 2005 (34)</td>
<td>82,911</td>
<td>Good</td>
<td>Average-risk women</td>
<td>≥2 tablets of non-ASA NSAIDs per wk for 20 y</td>
<td>CRC overall: 0.79 (0.64–0.97)&lt;br&gt;Colon cancer: 0.71 (0.56–0.91)&lt;br&gt;Rectal cancer: 1.04 (0.72–1.52)</td>
</tr>
<tr>
<td>North Jutland Population Database; Sørensen et al., 2003 (32)</td>
<td>183,693</td>
<td>Fair</td>
<td>Average-risk men and women</td>
<td>≥10 prescriptions for non-ASA NSAIDs over 9 y</td>
<td>Colon cancer: 0.7 (0.6–0.9)‡&lt;br&gt;Rectal cancer: 0.6 (0.4–0.9)‡</td>
</tr>
<tr>
<td>Tennessee Medicaid Program; Smalley et al., 1999 (33)</td>
<td>104,217</td>
<td>Fair</td>
<td>Elderly men and women</td>
<td>Regular use of non-ASA NSAIDs for ≥1 y</td>
<td>0.61 (0.48–0.77)</td>
</tr>
</tbody>
</table>

### Table 1. Chemopreventive Efficacy of Regular Use of Nonsteroidal Anti-inflammatory Drugs (NSAID)*

<table>
<thead>
<tr>
<th>Study, Year (Reference)</th>
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<th>Quality Score</th>
<th>Population</th>
<th>Dose and Duration</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case–control studies</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(n = 8)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>García-Rodríguez and Huerta-Alvarez, 2001 (22)</td>
<td>12,002</td>
<td>Good</td>
<td>Average-risk men and women</td>
<td>Regular use of non-ASA NSAIDs for ≥1 y</td>
<td>0.7 (0.63–0.78)</td>
</tr>
<tr>
<td>Slattery et al., 2004 (26)</td>
<td>4,403</td>
<td>Fair</td>
<td>Average-risk men and women</td>
<td>Regular use of non-ASA NSAIDs for ≥1 y</td>
<td>0.7 (0.6–0.8)</td>
</tr>
<tr>
<td>Kune et al., 1988 (23)</td>
<td>1,442</td>
<td>Fair</td>
<td>Average-risk men and women</td>
<td>Regular use of non-ASA NSAIDs for ≥1 y</td>
<td>0.77 (0.6–1.01)</td>
</tr>
<tr>
<td>Reeves et al., 1996 (25)</td>
<td>477</td>
<td>Fair</td>
<td>Average-risk women</td>
<td>Regular use of non-ASA NSAIDs for ≥1 y</td>
<td>0.43 (0.2–0.89)</td>
</tr>
<tr>
<td>Summary for the regular use of non-ASA NSAIDs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.7 (0.63–0.78)</td>
</tr>
<tr>
<td>Coogan et al., 2000 (29)</td>
<td>11,754 (in 4 separate studies)</td>
<td>Fair</td>
<td>Average-risk men and women</td>
<td>Regular use of any NSAID for ≥1 y</td>
<td>0.4 (0.2–0.9); 0.5 (0.4–0.7); 0.5 (0.3–0.9); and 0.7 (0.6–0.9)</td>
</tr>
<tr>
<td>Slattery et al., 2004 (26)</td>
<td>2,157</td>
<td>Fair</td>
<td>Average-risk men and women</td>
<td>Regular use of any NSAID for ≥1 y</td>
<td>0.8 (0.6–1.1)</td>
</tr>
<tr>
<td>Shaheen et al., 2003 (28)</td>
<td>1,308</td>
<td>Fair</td>
<td>Average-risk men and women</td>
<td>Regular use of any NSAID for ≥1 y</td>
<td>0.54 (0.39–0.75)</td>
</tr>
<tr>
<td>Peleg et al., 1996 (31)</td>
<td>505</td>
<td>Poor</td>
<td>Average-risk men and women</td>
<td>Regular use of any NSAID for ≥1 y</td>
<td>0.34 (0.12–0.94)</td>
</tr>
<tr>
<td>Muscat et al., 1994 (27)</td>
<td>1,011</td>
<td>Poor</td>
<td>Average-risk men and women</td>
<td>Regular use of any NSAID for ≥1 y</td>
<td>Men: 0.64 (0.42–0.97); women: 0.32 (0.18–0.57)</td>
</tr>
<tr>
<td>Summary for the regular use of any NSAID</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.57 (0.47–0.68)</td>
</tr>
</tbody>
</table>

**Table 1. Chemopreventive Efficacy of Regular Use of Nonsteroidal Anti-inflammatory Drugs (NSAID)***

<table>
<thead>
<tr>
<th>Study, Year (Reference)</th>
<th>Participants, (n)</th>
<th>Quality Score</th>
<th>Population</th>
<th>Dose and Duration</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Effects on the Incidence of colorectal adenomas</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PreSAP; Arber et al., 2006 (20)</td>
<td>933 vs. 628</td>
<td>Good</td>
<td>Higher risk (previous adenoma)</td>
<td>Celecoxib, 400 mg/d, for 3 y</td>
<td>Any adenoma: 0.64 (0.56–0.75) Advanced adenoma: 0.49 (0.33–0.73)</td>
</tr>
<tr>
<td>APC; Bertagnolli et al., 2006 (19)</td>
<td>685 vs. 671 vs. 679</td>
<td>Good</td>
<td>Higher risk (previous adenoma)</td>
<td>Celecoxib, 400 mg/d, for 3 y Celecoxib, 800 mg/d, for 3 y</td>
<td>Any adenoma: 0.67 (0.59–0.77) Advanced adenoma: 0.45 (0.33–0.63) Any adenoma: 0.43 (0.31–0.61) Advanced adenoma: 0.34 (0.24–0.50)</td>
</tr>
<tr>
<td>APPROVe; Baron et al., 2006 (18)</td>
<td>1158 vs. 1218</td>
<td>Good</td>
<td>Higher risk (previous adenoma)</td>
<td>Rofecoxib, 25 mg/d, for 3 y (N/A Canada)</td>
<td>Any adenoma: 0.76 (0.69–0.83) Advanced adenoma: 0.70 (0.58–0.86)</td>
</tr>
</tbody>
</table>

### Table 1. Chemopreventive Efficacy of Regular Use of Nonsteroidal Anti-inflammatory Drugs (NSAID) *

<table>
<thead>
<tr>
<th>Study, Year (Reference)</th>
<th>Participants, ( n )</th>
<th>Quality Score</th>
<th>Population</th>
<th>Dose and Duration</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cohort study ((n = 1))</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Polyp Prevention Study; Tangrea et al., 2003 (44)</td>
<td>1905</td>
<td>Good</td>
<td>Higher risk (previous adenoma)</td>
<td>Any NSAID use for 4 y</td>
<td>0.64 (0.48–0.85)</td>
</tr>
<tr>
<td>Case–control studies ((n = 8))</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Garcia-Rodríguez and Huerta-Alvarez, 2000 (38)</td>
<td>11 864</td>
<td>Good</td>
<td>Average-risk men and women</td>
<td>Regular use non-ASA NSAIDs for ≥1 y</td>
<td>0.7 (0.3–1.5)</td>
</tr>
<tr>
<td>Bigler et al., 2001 (35)</td>
<td>1502</td>
<td>Fair</td>
<td>Average-risk men and women</td>
<td>Regular use non-ASA NSAIDs for ≥1 y</td>
<td>0.4 (0.2–0.7)</td>
</tr>
<tr>
<td>Logan et al., 1993 (36)</td>
<td>300</td>
<td>Fair</td>
<td>Average-risk men and women</td>
<td>Regular use non-ASA NSAIDs for ≥1 y</td>
<td>0.56 (0.3–1.2)</td>
</tr>
<tr>
<td>Boyapati et al., 2003 (37)</td>
<td>405</td>
<td>Poor</td>
<td>Average-risk men and women</td>
<td>Regular use non-ASA NSAIDs for ≥1 y</td>
<td>0.4 (0.2–0.7)</td>
</tr>
<tr>
<td>Summary for the regular use of non-ASA NSAIDs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.55 (0.4–0.76)</td>
</tr>
<tr>
<td>Martin et al., 2002 (43)</td>
<td>719</td>
<td>Good</td>
<td>Average-risk men and women</td>
<td>Regular use any NSAIDs for ≥1 y</td>
<td>0.5 (0.3–0.8)</td>
</tr>
<tr>
<td>Martinez et al., 1995 (41)</td>
<td>637</td>
<td>Good</td>
<td>Average-risk men and women</td>
<td>Regular use any NSAIDs for ≥1 y</td>
<td>0.46 (0.29–0.75)</td>
</tr>
<tr>
<td>Lieberman et al., 2003 (42)</td>
<td>1770</td>
<td>Fair</td>
<td>Average-risk men and women</td>
<td>Regular use any NSAIDs for ≥1 y</td>
<td>0.67 (0.5–0.89)</td>
</tr>
<tr>
<td>Logan et al., 1993 (36)</td>
<td>300</td>
<td>Fair</td>
<td>Average-risk men and women</td>
<td>Regular use any NSAIDs for ≥1 y</td>
<td>0.33 (0.1–1.4)</td>
</tr>
<tr>
<td>Peleg et al., 1996 (31)</td>
<td>525</td>
<td>Poor</td>
<td>Average-risk men and women</td>
<td>Regular use any NSAIDs for ≥1 y</td>
<td>0.56 (0.2–1.52)</td>
</tr>
<tr>
<td>Summary for the regular use of any NSAID</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.57 (0.46–0.71)</td>
</tr>
</tbody>
</table>

Ongoing Trials

- With key words “colorectal NSAID” and “colorectal chemoprevention”
- 57 search results
- 10 are currently addressing the question of cancer risk reducing intervention (CRRI) with non-ASA NSAIDS for colorectal cancer

Source: clinicaltrials.gov
Discussion

- Selective Cox-2 inhibitors inhibit antithrombotic prostacyclin (PGI) while Cox-1 continues to produce thromboxane A, enhanced thrombosis, and increased serious cardiac events in the Cox-2 treatment arm. Selective Cox-2 inhibitors are too toxic for CRRI.

- Mixed Cox inhibitors (piroxicam, indomethacin, aspirin) have sufficient gastrointestinal toxicity to reduce their acceptability as CRRIs.

- The United States Preventive Services Task Force instead recommends adherence to current colorectal cancer screening recommendations (fecal occult blood testing and endoscopy).

Thank you
References

- Lai GH, Zhang Z, Sirica AE. Celecoxib acts in a cyclooxygenase-2-independent manner and in synergy with emodin to suppress rat cholangiocarcinoma growth in vitro through a mechanism involving enhanced Akt inactivation and increased activation of caspases-9 and -3. Mol Cancer Ther 2003;2:265. [PMID: 12657721]
Air Pollution and Cancer

Nicholas Winters
Division of Experimental Medicine
EPIB 671
May 30, 2013
Contents

- Introduction to air pollution
  - Components of air pollution and cities with highest concentrations
  - Chronic illness associated with air pollution
  - Components that are known carcinogens
  - Downfalls and advances in exposure assessment
    - Satellite mapping
    - LUR mapping

- Associations with cancer

- Future research
Components of Air Pollution

Air pollution comprises several components:

- Particulate Matter; <10um and <2.5um (PM$_{10}$ and PM$_{2.5}$)
- PM$_{10}$: Pollen, spores, bacteria, dust, viruses
- PM$_{2.5}$: combustion products
- Nitrogen dioxide (NO$_2$)
- Sulfur dioxide (SO$_2$)
- Carbon oxides (CO, CO$_2$)
- Volatile Organic Compounds (Benzene, Chlorofluorocarbons)
### IARC Carcinogens in Air Pollution (from traffic emissions)

<table>
<thead>
<tr>
<th>Agent</th>
<th>IARC Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzene</td>
<td>1</td>
</tr>
<tr>
<td>Formaldehyde</td>
<td>1</td>
</tr>
<tr>
<td>Soot / PM (from exhaust)</td>
<td>1</td>
</tr>
<tr>
<td>Perchloroethylene</td>
<td>2A</td>
</tr>
<tr>
<td>Dichloromethane</td>
<td>2B</td>
</tr>
</tbody>
</table>

IARC monographs: [http://monographs.iarc.fr/ENG/Classification/ClassificationsGroupOrder.pdf](http://monographs.iarc.fr/ENG/Classification/ClassificationsGroupOrder.pdf)
Pollution levels around the world

- Highest pollution – Beijing, Delhi, and Mexico City
- Total suspended particulates (TSP)
  - Beijing: 600 ug m$^{-3}$
  - Montreal: 120 ug m$^{-3}$

Image – The Economist; daily chart “Choked”.
Beijing, China

Two photos of the same view of the China World Trade Centre Tower III taken only a few days apart.

Photo: The Washington Post – Bill Bishop
Montreal, Canada

Aug 14, 2002 – PM$_{2.5}$ 37 ug m$^{-3}$

Aug 27, 2002 – PM$_{2.5}$ 3 ug m$^{-3}$

Goldberg, M. - lecture slides ENVR 610
Chronic Illnesses and Air Pollution

- Increased risks have been associated with the following chronic illnesses:
  - Asthma morbidity\(^1\)
  - Death from coronary heart disease\(^2\)
  - Non-accidental mortality\(^2\)
  - Death from chronic obstructive pulmonary disease\(^3\)
  - Death from type II diabetes\(^4\)

- Are there associations with cancer?

Problems With Exposure

- Assigning individual exposures has been difficult - areas 50m apart can have differences in NO\textsubscript{2} of up to 30µg m\textsuperscript{-3}

- Studies use strange, inaccurate, and completely meaningless exposure metrics.

Examples:

- **The inaccurate**: many studies use distance from highways, traffic frequency, or even gas station densities.

- **The strange**: a study used number of petrochemical employees per municipality / population of that municipality = individual exposure.

- **The completely meaningless**: a study used pollution data from 1999 - 2000 to assess exposure for leukemia cases diagnosed from 1949 - 1980 (20 years after the last diagnosis!).
Improving Exposure Assessments

- Ogawa passive air samplers for $\text{NO}_2 \text{SO}_2$
- Satellite data for $\text{PM}_{2.5}$ MODIS and/or MISR

Improving Exposure Assessments

Land Use Regression models (LURs) - how to build them:
- Specific $[\text{NO}_2]$ from Ogawa filters are collected = dependent variable
- Traffic density, land use, topography, and wind conditions of area are determined = independent variables for the model.
- Model is used to predict $[\text{NO}_2]$ in areas without samplers.

Samplers + Traffic density + L and use + Wind speed/ direction = LUR
LUR of Montreal

Image: Crouse, D. (2009) A prediction-based approach to modelling temporal and spatial variability of traffic-related air pollution in Montreal, Canada
What associations with cancer have been found?
# Pollution Related Cancer Findings

<table>
<thead>
<tr>
<th>Air Pollutant</th>
<th>Cancer Site</th>
<th>Exposure</th>
<th>Effect measure (95% confidence interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \text{NO}_2, \text{SO}<em>2, \text{PM}</em>{2.5} )</td>
<td>Lung (incidence)(^2)</td>
<td>Never smokers</td>
<td>OR 1.47 (1.01 - 2.16)</td>
</tr>
<tr>
<td>( \text{PM}_{2.5} )</td>
<td>Lung (mortality from)(^1)</td>
<td>Per 10 ug m(^{-3})</td>
<td>OR 1.15 (1.06 - 1.24)</td>
</tr>
<tr>
<td>( \text{NO}_2 )</td>
<td>Post-menopausal breast cancer (incidence)(^6)</td>
<td>Per 5 ppb</td>
<td>OR 1.31 (1.00 - 1.71)</td>
</tr>
<tr>
<td>( \text{NO}_2 )</td>
<td>Prostate Cancer (incidence)(^7)</td>
<td>Per 5 ppb</td>
<td>OR 1.44 (1.21 - 1.73)</td>
</tr>
</tbody>
</table>
Reviews have shown that occupational benzene exposures have increased a person’s risk of leukemia – 10 ppm lifetime occupational exposure is responsible for 50 excess deaths due to leukemia per 1000 people.\(^8\)

My research:

- Exposure assessment: satellite based concentrations of PM\(_{2.5}\) and NO\(_2\)
- Design: case-control study – 424 female and 642 male leukemia cases using the National Enhanced Cancer Surveillance System (NECS).
- Objective: determine whether there is an association between daily exposure to ambient air pollution and incidence of leukemia.


5. R. Beelen et al., Long-term exposure to traffic-related air pollution and lung cancer risk. Epidemiology 19, 702 (Sep, 2008).


Exploring the association between HPV and bladder cancer

EPIB-671  Cancer Epidemiology

Livia Florianova
PGY-1 Anatomical Pathology
May 31, 2013
Bladder cancer

- Most common malignancy involving the urinary system
- 9th most common malignancy worldwide
- More common in industrialized countries (90% TCC)
- 3 M : 1 F

**ESTABLISHED RISK FACTORS:**

- **Cigarette smoking** (even 20+ years after cessation)
- Industrial exposure to aromatic amines
- Middle East, Africa: *Schistosoma haematobium* infection (squamous cell carcinoma in 70%)
- Chronic cystitis

TCC : transitional cell carcinoma
HPV

- Double-stranded DNA virus that infects the stratified epithelium of the skin and mucosae
- Causes benign and malignant tumors of epithelial origin

- > 100 types with different tissue tropism:
  - cutaneous (ex: 1, 2, 4, etc.): plantar / butcher’s warts
  - anogenital (ex: 6, 11, 16, 18, etc.): genital warts, CIN
  - other mucosal surfaces (ex: 6, 11, 16, etc.): oral, respiratory

HPV integrates its DNA into host cells

[koilocytosis, nuclear enlargement, multinucleation, prominent nucleoli]
HPV in bladder cancer etiology

- HPV shows a particular tropism for squamous epithelium of different mucosal sites
- Urothelium lines renal pelvis, ureters, bladder, urethra; intermediate between nonkeratinizing squamous and pseudostratified columnar epithelium

- Urethra considered as a reservoir for the virus
- Proximity of the urethra and bladder facilitates transmission

- HPV 6 & 11 found in condylomata acuminata of the bladder
- Urothelial malignancies have been reported in association with extensive urethral and bladder condylomata

(Libby et al., J Urol 1985)
Studies’ overview

- Earliest publications from early 1990’s
- Study types: case-control or case series
- Number of cases: between 50-100 pts, often < 50
- Patient population: M >>>> F (often > 80 %)
- TCC as main histological type
- Sampling: transurethral, open cystectomy, urine, serum
- Tissues: fixed, frozen
- HPV detection:
  - PCR, RT-PCR
  - DNA (Southern blot, dot blot, ISH, restr. frag. length polymorph.)
  - Protein-based (Western blot, ELISA)
Early studies

- HPV 6/11, 16/18 or 31/33 in 4/20 bladder tumors (Southern blot) (Shibutani et al., Urology 1992)

- HPV 16/18 in 12/76 TCCs (ISH in formalin-fixed tissues) (Bryant et al., Brit J Urol 1991)

- HPV 16/18 significantly ↑ in tumors (62%) than controls (14%) (PCR on paraffin-embedded tissues) (Anwar et al., Cancer 1992)

However:

- Variable incidence (2.5-81%) of high-risk HPV in larger series of TCCs (Lopez-Bertran et al., Biomed & Pharmacother 1997, review)

- No HPV (various types) found in 57 TCCs (PCR, Southern blot) HPV 6 detected in 1 bladder papilloma (Aynaud et al., J Urol 1998)
More recent studies

- HPV-16 in 27/27 bladder cancers due to Schistosoma detected in tumor and serum (qPCR)
  
  (Yang et al., PNAS 2005)

- HPV in 15/99 (15%) bladder cancers + Trend of high-grade tumors having a higher infection rate, overall and for high-risk HPV types (PCR on bladder washes)
  
  (Moonen et al., Eur Urol 2007)

- High-risk HPV in both tumor and urine samples of TCCs when compared to controls (PCR)
  
  (Cai et al., Oncol Rep 2011)

- HPV (not types 16 nor 18) in only 7/124 cases and 5/151 controls by PCR on urine
  
  (Polesel et al., Br J Cancer 2012)
Regional studies

- **Egypt**: HPV 16/18 detected in 1/114 bladder carcinomas, with 58% being TCC (ISH in formalin-fixed tissues)  
  (El A Helal et al., Pathol Oncol Res 2006)

- **Greece**: No HPV in 30 TCCs and controls taken from same patient (qPCR)  
  (Panagiotakis et al., Tumor Biol 2013)

- **Tunisia**: No low nor high risk HPV in 125 TCCs (PCR)  
  (Ben Selma et al., Pathol Res Pract 2010)

- **Egypt**: 60 cases-controls: HPV 16/18/52 significantly associated with invasive TCC, Schistosoma infection and recurrence tendency. Healthy controls negative for HPV 16/18 serology but 9.5% of HPV 16 negative pts by PCR were serum Ab positive.  
  (Badawi et al., Medscape J Med 2008)
Meta-analyses

(Gutierrez et al., J Urol 2006)

- Moderate but inconclusive link between HPV and bladder cancer (cannot establish HPV as etiological factor).

- Finding a relationship between bladder cancer and human papillomavirus depends on the method used.

- Studies often use insufficient number of cases and controls (some have no controls at all).

- Using a combination of various microbiological techniques in a single subject and for a sufficient number of cases compared to controls will be required for future studies.

PCR studies: pooled OR = 2.7 (1.5-4.6)
DNA based studies: pooled OR = 0.7 (0.1-3.9)
Non-DNA (protein) based studies: pooled OR = 2.9 (1.7-5.3)
Meta-analyses

(Li et al., J Infect Dis 2011)

- Clear link between bladder cancer and HPV infection, although the risk estimates may vary by HPV type, study region, histological type, detection method, HPV DNA source.

- 926 cases, 219 controls: pooled OR = 2.84 (1.39-5.8)

- The sensitivity of HPV detection varied due to amplification efficiency between different types of HPV primers, especially in paraffin-embedded tissue samples.

- Difficult to estimate the sex differences in HPV prevalence and risk of bladder cancer since few studies presented HPV prevalence data in bladder cancer cases stratified by sex.
## Meta-analyses

Table 4. Meta-analysis of 19 Case-Control Studies on the Risk of Bladder Cancer With Human Papillomavirus (HPV) Infection, Stratified by HPV Type, Region, Histological Type, Detection Method, HPV DNA Specimen, and Publication Calendar Period

<table>
<thead>
<tr>
<th>Variable</th>
<th>No. of studies</th>
<th>$\chi^2$ for heterogeneity</th>
<th>$P$ for heterogeneity</th>
<th>Model selected</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>19</td>
<td>38.66</td>
<td>.001</td>
<td>Random</td>
<td>2.84 (1.39-5.80)</td>
</tr>
<tr>
<td><strong>HPV type</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High-risk type$^a$</td>
<td>16</td>
<td>27.27</td>
<td>.004</td>
<td>Random</td>
<td>3.48 (1.28-9.44)</td>
</tr>
<tr>
<td>Low-risk type$^b$</td>
<td>16</td>
<td>12.75</td>
<td>.03</td>
<td>Random</td>
<td>1.04 (0.33-3.24)</td>
</tr>
<tr>
<td><strong>Related to HPV-16</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>15</td>
<td>8.02</td>
<td>.53</td>
<td>Fixed</td>
<td>5.74 (2.59-12.71)</td>
</tr>
<tr>
<td>No</td>
<td>15</td>
<td>3.62</td>
<td>.94</td>
<td>Fixed</td>
<td>2.93 (1.74-4.93)</td>
</tr>
<tr>
<td><strong>Region</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Europe</td>
<td>8</td>
<td>1.42</td>
<td>.92</td>
<td>Fixed</td>
<td>5.19 (2.01-13.40)</td>
</tr>
<tr>
<td>North America</td>
<td>4</td>
<td>18.11</td>
<td>&lt;.001</td>
<td>Random</td>
<td>1.64 (0.10-26.57)</td>
</tr>
<tr>
<td>Asia</td>
<td>6</td>
<td>6.19</td>
<td>.29</td>
<td>Fixed</td>
<td>3.79 (2.26-6.35)</td>
</tr>
<tr>
<td><strong>Histological type</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TCC</td>
<td>15</td>
<td>36.71</td>
<td>&lt;.001</td>
<td>Random</td>
<td>3.17 (1.27-7.98)</td>
</tr>
<tr>
<td>Other$^c$</td>
<td>9</td>
<td>4.50</td>
<td>.61</td>
<td>Fixed</td>
<td>2.28 (1.05-4.94)</td>
</tr>
<tr>
<td><strong>HPV DNA specimen</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fixed tissue</td>
<td>10</td>
<td>6.98</td>
<td>.54</td>
<td>Fixed</td>
<td>3.79 (2.32-6.20)</td>
</tr>
<tr>
<td>Fresh tissue</td>
<td>6</td>
<td>2.73</td>
<td>.60</td>
<td>Fixed</td>
<td>6.35 (1.83-21.99)</td>
</tr>
<tr>
<td><strong>HPV DNA detection method</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PCR-based</td>
<td>16</td>
<td>9.62</td>
<td>.7</td>
<td>Fixed</td>
<td>4.28 (2.74-6.70)</td>
</tr>
<tr>
<td>Broad-spectrum primers</td>
<td>4</td>
<td>1.12</td>
<td>.57</td>
<td>Fixed</td>
<td>5.12 (0.97-26.98)</td>
</tr>
<tr>
<td>Type-specific primers</td>
<td>8</td>
<td>7.53</td>
<td>.28</td>
<td>Fixed</td>
<td>4.34 (2.59-7.27)</td>
</tr>
<tr>
<td>Combination of both primers</td>
<td>4</td>
<td>0.91</td>
<td>.82</td>
<td>Fixed</td>
<td>3.64 (1.26-10.50)</td>
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<tr>
<td>Non-PCR-based</td>
<td>3</td>
<td>4.69</td>
<td>.10</td>
<td>Fixed</td>
<td>0.64 (0.23-1.76)</td>
</tr>
<tr>
<td><strong>Publication date</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1990–1999</td>
<td>15</td>
<td>34.73</td>
<td>.001</td>
<td>Random</td>
<td>2.44 (1.07-5.57)</td>
</tr>
<tr>
<td>2000–2010</td>
<td>4</td>
<td>0.63</td>
<td>.89</td>
<td>Fixed</td>
<td>6.41 (1.77-23.16)</td>
</tr>
</tbody>
</table>

(Li et al., J Infect Dis 2011)
**Meta-analyses**

(Jimenez-Pacheco et al., Korean J Urol 2012)

- **Clear and moderate association between virus exposure and the presence of bladder cancer.**

- **Pooled OR = 2.13 (1.54-2.95)**

  - PCR studies: pooled OR = **2.4** (1.5-3.8)
  - DNA based studies: pooled OR = **0.84** (0.2-3.3)
  - Non-DNA (protein) based studies: pooled OR = **2.1** (1.8-3.5)

- **Homogeneity of data (Chi-square analysis).**
Points to consider

- No clear evidence that HPV is an initiator of bladder cancer: tumor could be secondarily colonized by HPV
- Sensitivity of HPV detection depends on technical factors (type of technology, type of PCR primers, quality of DNA for PCR, frozen VS fresh tissues)
- Long lag time from HPV infection to antibody seroconversion could explain the possibility of undetectable levels of serum antibodies
- Discrepancy between serum Ab & DNA detection: sampling misses site(s) of infection, which could be focal
- Contamination issues during sampling (trans-urethral method)
- Appropriate control groups lacking
- Men and women unequally represented
- No statistical control of main confounding factors: smoking, industrial exposure, sexual practice, Schistosoma infection
Criteria to establish causality

- **Experimental evidence**: weak.
- **Strength of association**: moderate and variable.
- **Consistency**: no, and confounding factors not analyzed.
- **Temporality**: no data.
- **Biological gradient**: ??... Rare studies showing HPV 16/18 associated with invasive or high grade tumors.

- **Biological plausibility**: yes (type of epithelium at risk, observed papillary lesions in the bladder)
Conclusion

- Weak body of evidence to associate HPV and bladder cancer
- Cannot yet determine if there is a role for HPV in bladder cancer tumorigenesis
- Future case-control studies need to analyze confounding factors and have stronger control groups
- Studies needed on the association of bladder cancer and HPV in women
- Follow recommended protocols for HPV detection
References

COLORECTAL CARCINOMA
AND
ULCERATIVE COLITIS

DOMINIQUE BOUDREAU
SURGICAL ONCOLOGY FELLOW
MAY 31 2013
1- Sporadic colorectal cancer

2- Ulcerative colitis-associated colorectal cancer

3- Low-grade dysplasia and cancer
Third most commonly diagnosed cancer (worldwide) in males and second in females

Follows a adenoma-carcinoma sequence
  - Early APC mutation
  - Later p53 mutation

Source: GLOBOCAN 2008
1- Sporadic colorectal cancer

2- Ulcerative colitis-associated colorectal cancer

3- Low-grade dysplasia and cancer
Ulcerative colitis

- Inflammatory bowel disease
- Limited to the mucosa of the colon generally starting in the rectum and extending proximally

Treatment

- Medical (steroids, 5-ASA analogs, immunosuppressors, biologic agents)
- Surgical (proctocolectomy)

- Associated with a greater risk of CRC than population
UC-ASSOCIATED COLORECTAL CANCER

Risk factors

- Severity/extent of inflammation
- Duration of UC
- Concomittant primary sclerosing cholangitis
- Family history of CRC

Triantafillidis, Anticancer research, 29(7), 2727–2737.
• American Cancer Society guidelines
  ~ Colonoscopy q 1-2 years
  ~ After 8 years if pancolitis
  ~ After 12-15 years if left colitis
Early estimates: higher proportion of more advanced disease (hospital-based studies)
Later population-based studies
General CRC risk estimation:
  - Between 0.9 and 8.8-fold (limited colitis)
  - Between 0.8 and 23-fold (pancolitis)

Triantafillidis, Anticancer research, 29(7), 2727–2737.
UC-ASSOCIATED COLORECTAL CANCER

- Eaden et al., Amer J Gastroenterol, 2001, 95: 2710-2719
  (54,000 patients)
  - 2% at 10 years
  - 8% at 20 years
  - 18% at 30 years

- Danish cohort study (population-based)
- Cumulative risk:
  - 0.4% after 10 years
  - 1.1% after 20 years
  - 3.1% after 30 years
  - Lifetime risk 3.5% vs 3.1% for Danish population
How can we explain that difference???

<table>
<thead>
<tr>
<th>Eaden et al.</th>
<th>Winther et al.</th>
</tr>
</thead>
<tbody>
<tr>
<td>2% at 10 years</td>
<td>0.4% at 10 years</td>
</tr>
<tr>
<td>8% at 20 years</td>
<td>1.1% at 20 years</td>
</tr>
<tr>
<td>18% at 30 years</td>
<td>3.1% at 30 years</td>
</tr>
</tbody>
</table>
Winther et al.

- Population-based
- Systematic use of 5-ASA maintenance treatment
- High rates of surveillance colonoscopy
- High rates of proctocolectomy
  - 24% after 10 years
  - 32.4% after 25 years
- CRC risk factors in Danish population?
- Less aggressive disease?
1- Sporadic colorectal cancer

2- Ulcerative colitis-associated colorectal cancer

3- Low-grade dysplasia and cancer
UC-associated Dysplasia

Inflammatory Bowel Disease-Dysplasia Morphology Study Group

- Negative
- Indefinite
- Positive
  - High grade = colectomy
    - Cancer risk 42% at colectomy (Bernstein, Lancet. 1994;343(8889):71)
  - Low grade = controversy...
    - Confirmation by a second pathologist
    - Surveillance (colonoscopy) VS
    - Surgery (proctocolectomy)
**UC-associated Dysplasia**

- Few patients
- Heterogenous population
- Various diseases
- Different treatments

<table>
<thead>
<tr>
<th>Percentage/Progression</th>
<th>Description</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>19 percent (3 of 16)</td>
<td>had CRC at immediate colectomy</td>
<td>Bernstein, Lancet 1994</td>
</tr>
<tr>
<td>34 percent (26 of 77)</td>
<td>had CRC at colectomy at 12 months</td>
<td>Gorfine, DCR 2000</td>
</tr>
<tr>
<td>50 percent (9 of 18)</td>
<td>progressed to a more advanced lesion at a median of 32 months</td>
<td>Ullman, Am J Gastroenterol. 2002</td>
</tr>
<tr>
<td>10 percent (3 of 29)</td>
<td>progressed to a more advanced lesion at 10 years</td>
<td>Lim, Gut., 2003</td>
</tr>
<tr>
<td>15 percent (7 of 46)</td>
<td>progressed to CRC at five years</td>
<td>Ullman, Gastroenterology, 2003</td>
</tr>
</tbody>
</table>
Mixed studies, some done on non-UC population (NSAIDs and Calcium)

- ASA / NSAIDs
- 5-ASA
- Calcium
- Statins
- Infliximab (Remicade)
- Ursodiol
- Smoking
Testing for the Presence of Positive-Outcome Bias in Peer Review

A Randomized Controlled Trial

Gwendolyn B. Emerson, MD; Winston J. Warme, MD; Fredric M. Wolf, PhD; James D. Heckman, MD; Richard A. Brand, MD; Seth S. Leopold, MD

Background: If positive-outcome bias exists, it threatens the integrity of evidence-based medicine.

Methods: We sought to determine whether positive-outcome bias is present during peer review by testing whether peer reviewers would (1) recommend publication of a “positive” version of a fabricated manuscript over an otherwise identical “no-difference” version, (2) identify more purposefully placed errors in the no-difference version, and (3) rate the “Methods” section in the positive version more highly than the identical “Methods” section in the no-difference version. Two versions of a well-designed randomized controlled trial that differed only in the direction of the finding of the principal study end point were submitted for peer review to 2 journals in 2008-2009. Of 238 reviewers for The Journal of Bone and Joint Surgery and Clinical Orthopaedics and Related Research randomly allocated to review either a positive or a no-difference version of the manuscript, 210 returned reviews.

Results: Reviewers were more likely to recommend the positive version of the test manuscript for publication than the no-difference version (97.3% vs 80.0%, P < .001). Reviewers detected more errors in the no-difference version than in the positive version (0.85 vs 0.41, P < .001). Reviewers awarded higher methods scores to the positive manuscript than to the no-difference manuscript (8.24 vs 7.53, P = .005), although the “Methods” sections in the 2 versions were identical.

Conclusions: Positive-outcome bias was present during peer review. A fabricated manuscript with a positive outcome was more likely to be recommended for publication than was an otherwise identical no-difference manuscript.

Arch Intern Med. 2010;170(21):1934-1939