Opioids, Aspirin, NSAIDs, sCOX-2 Inhibitors & Breast Cancer Recurrence:
Pharmacoepidemiology studies using DBCG data

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"Pharmacoepidemiology"

- The study of drug use or the effect of drugs in large populations

- Several pharmacoepi databases in Denmark:
  - Enable compilation of longitudinal drug histories &
  - Linkage of prescription data to other population-based registries in Denmark, *e.g.*, *DBCG*
Pharmacoepi databases in Denmark

- **The Prescription Registries of the Northern and Central Danish Region** (Aarhus University – AUPD ~1989+; nationwide 2005+)
- **The Odense University Pharmacoepidemiological Database** (OPED – 1990+, South & East Dk ~2007+)
- **The Danish National Prescription Registry (DNPR)** at Statistics Denmark (1995+)

**Main difference:**
- AUPD & OPED: possibility to identify drug users
- DNPR: de-identified via Stats Dk
A Cancer Treatment in Your Medicine Cabinet?

By MICHELLE HOLMES and WENDY CHEN  MAY 19, 2014

WE believe that it might be possible to treat breast cancer — the leading cause of female cancer death — with a drug that can already be found in nearly every medicine cabinet in the world: Aspirin.

In 2010, we published an observational study in The Journal of Clinical Oncology showing that women with breast cancer who took aspirin at least once a week for various reasons were 50 percent less likely to die of breast cancer. In 2012, British researchers publishing results of
Pharmacoepi studies using DBCG – some examples
Low-dose Aspirin, NSAIDs, Selective COX-2 Inhibitors & Breast Cancer Recurrence: a Danish population-based cohort study

Deirdre Cronin-Fenton, Uffe Heide-Jørgensen, Thomas P Ahern, Timothy L Lash, Peer Christiansen, Bent Ejlertsen, Henrik T Sørensen

Epidemiology, in press 2015 (scheduled for July 2016)
Epidemiological studies

- Inconsistent findings
- Post-diagnostic aspirin = 50% reduction in breast cancer mortality?
- Pre-diagnostic aspirin use = 20% reduction?
- NSAIDs = inconsistent findings
- sCOX-2i = previous studies?
- Few adjusted for statin use
Aim:
• To investigate the association of aspirin, NSAIDs, and sCOX-2i use, with breast cancer recurrence

Hypothesis:
• Prescription use of these drugs is associated with a decreased rate of breast cancer recurrence compared with non-use of the drugs
Danish Breast Cancer Cooperative Group

Danish National Registry of Patients

Clinical Registry
Clinical, tumor, treatment data
Breast cancer recurrence

1976+

National Prescription Registry (Stats Dk)

1994+
Aspirin, NSAIDs, sCOX-2i prescriptions
Simvastatin
Prediagnostic HRT (Opioids, etc.)

1968+

Danish Civil Registry

1977+
Hospital discharge registry
Comorbid diseases

1968+
Emigration
Vital status

Danish
Breast
Cancer
Cooperative
Group
Study Population

• Cohort of stage I-III breast cancer patients in Denmark

• Diagnosed 1996-2008 & registered in DBCG

• Follow-up for breast cancer recurrence in the DBCG registry (i.e., local, regional, distant recurrent disease or contralateral breast cancer)

• 10 years of follow-up or through 01/01/2013
Prescription drugs: Exposure and Confounder definition

Low-dose aspirin, NSAIDs, sCOX2 inhibitors

• >=1 prescription each year, updated daily & lagged by one year

• ”New users”: >=5 years prescription history, no pre-diagnostic use

• Dose-response: number of prescriptions

• Pre-diagnostic use: women with >=2 years prescription history

• Comedications: post-diagnostic time-varying use of simvastatin & pre-diagnosis HRT
Statistical Analyses

- Crude and adjusted Cox proportional hazards regression models with time-varying drug exposure updated yearly & lagged by one year

- Sensitivity analyses:
  - Drug exposure lagged by two years
  - >=2 prescriptions

- Stratified analyses (stage & ER status)
- Site of recurrence
Results

- N=34,188 breast cancer patients
- 17% aspirin users (>=1 prescription)
- 42% NSAIDs users
- 17% sCOX-2 inhibitors

- Median age = 58 years

Aspirin users (vs non-users): older, more often mastectomy
NSAID users & sCOX-2i users: slightly higher proportion stage I
Aspirin, NSAID, sCOX-2i users: more likely to have received simvastatin

- 5,325 recurrences in 233,130 PY
- Median follow-up = 7.1 yrs
Opioids and breast cancer recurrence: A Danish population-based cohort study

Deirdre P. Cronin-Fenton PhD1,*, Uffe Heide-Jørgensen PhD1, Thomas P. Ahern PhD2, Timothy L. Lash DSc1,3, Peer M. Christiansen MD, DMSoc4,5, Bent Ejlertsen MD, PhD5,6, Per Sjøgren MD, DMSoc7, Henrik Kehlet MD, PhD8 and Henrik T. Sørensen MD, DMSoc1

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Background

- Increasing opioid use
- Opioids inhibit cell-mediated immunity
- Lab models: opioids promote/negate tumour growth
- Humans: Poorer survival associated with morphine-based anaesthesia?
- The potential that opioids may exacerbate malignant disease requires clarification
Prescription drugs: Exposure and Confounder definition

Opioid prescriptions
• >=1 prescription each year, updated daily & lagged by one year
  – *i.e., a patient was considered exposed to opioids at a given time when she was prescribed an opioid >1 yr but <2 yrs before each assessment period*

• Opioid strength:
  *Weak opioids* = tramadol, codeine, dextropropoxyphene;
  *Strong opioids* = all others

• **Immunosuppressive effect** (*Sacerdote, 2006*)

• **Chronic long-term use**: >=1 opioid prescription per month for >=6 months of the prescribing year

• **Morphine equivalent dose** (*Jarlbaek et al, 2005*)

• **Comedications**: post-diagnostic time-varying use of simvastatin & pre-diagnosis HRT
**Exposure**

<table>
<thead>
<tr>
<th>Category</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Opioid use</td>
<td>1.00 (0.91, 1.09)</td>
</tr>
<tr>
<td><strong>Strength of Opioid Exposure</strong></td>
<td></td>
</tr>
<tr>
<td>Only weak opioids</td>
<td>1.00 (0.91, 1.09)</td>
</tr>
<tr>
<td>Only strong opioids</td>
<td>0.95 (0.76, 1.19)</td>
</tr>
<tr>
<td>Both weak and strong opioids</td>
<td>0.95 (0.75, 1.20)</td>
</tr>
<tr>
<td><strong>Cumulative Opioid Use, morphine equivalents</strong></td>
<td></td>
</tr>
<tr>
<td>Low: 1 to &lt;=500</td>
<td>1.10 (1.00, 1.21)</td>
</tr>
<tr>
<td>Medium &gt;501 to &lt;=5000</td>
<td>0.98 (0.88, 1.09)</td>
</tr>
<tr>
<td>High &gt;5000</td>
<td>0.96 (0.84, 1.10)</td>
</tr>
<tr>
<td><strong>Opioid exposure by immunosuppressive effect</strong></td>
<td></td>
</tr>
<tr>
<td>Strongly immunosuppressive</td>
<td>0.75 (0.57, 0.99)</td>
</tr>
<tr>
<td>Weakly immunosuppressive</td>
<td>1.00 (0.92, 1.08)</td>
</tr>
<tr>
<td>Other</td>
<td>1.00 (0.86, 1.16)</td>
</tr>
<tr>
<td><strong>Chronicity of opioid use</strong></td>
<td></td>
</tr>
<tr>
<td>Chronic long-term use</td>
<td>1.10 (0.90, 1.35)</td>
</tr>
<tr>
<td>Short-term use</td>
<td>0.99 (0.90, 1.09)</td>
</tr>
</tbody>
</table>
Strengths

- Large size & prospective data collection
- High quality registry data
- Information on clinical factors & complete follow-up
- Outcome of recurrence rather than mortality
  - Specific effect of drugs on breast cancer, as distinct from mortality
- Adjustment for potential confounding due to simvastatin
Limitations

• Prescription compliance
  – Redeemed prescriptions

• No information on in-hospital or perioperative drug use

• Over-the-counter drug use
Conclusions & Perspectives

• No evidence of an association between post-diagnostic use of opioids, aspirin, NSAIDs, or sCOX-2i prescriptions and the rate of breast cancer recurrence.

• Use of pre-diagnostic aspirin, NSAIDs or sCOX2-inhibitors & recurrence warrants further investigation.

• Important findings to the increasing numbers of people faced with decisions regarding treatment for pain.
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Figure courtesy of Rikke N. Pedersen
Background

- Aspirin, NSAIDs, and selective COX-2 inhibitors (sCOX-2i)
  - Analgesics, anti-inflammatories, anti-pyretics
  - Pleiotropic effects: cardiovascular disease & cancer prevention
  - Target COX-1 & COX-2, which promote angiogenesis & prevent apoptosis
  - Lab studies: drugs impede breast cancer cells growth
  - Aspirin: low-dose has anti-platelet effects; high-dose has prostaglandin inhibitory effects
  - NSAIDs & sCOX-2: anti-prostaglandin effects
Pharmaco-epidemiologic research using the DBCG database

Original Article

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Epidemiology

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