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

Deirdre Cronin Fenton
Associate Professor, Ph.D.
dc@clin.au.dk

DBCG Annual Meeting, January 2016

”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*

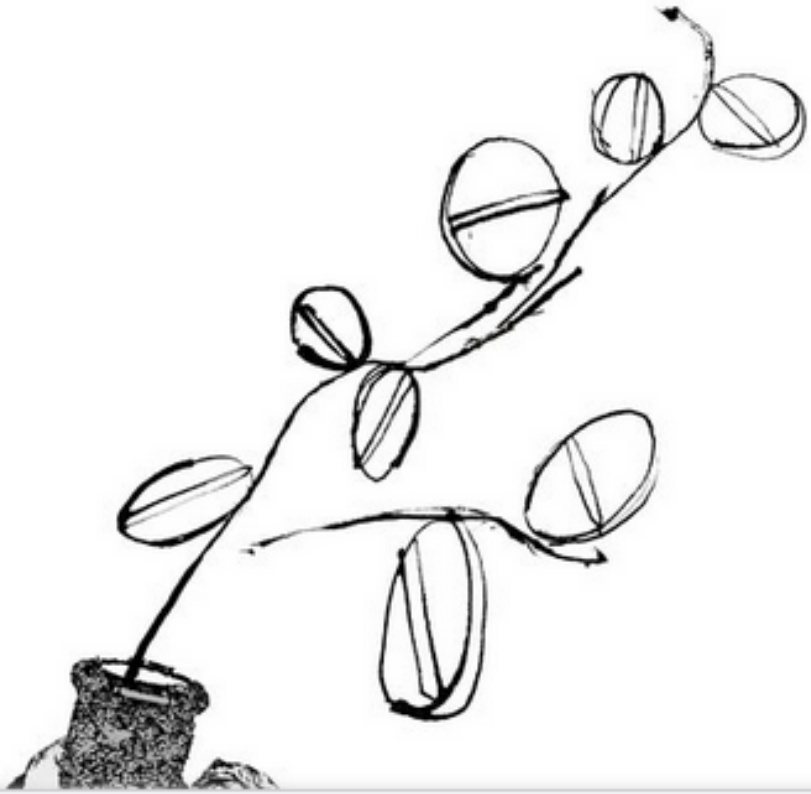
Pharmacoepi databases in Denmark

- **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

The New York Times

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

Pharmacoepi studies using DBCG – some examples

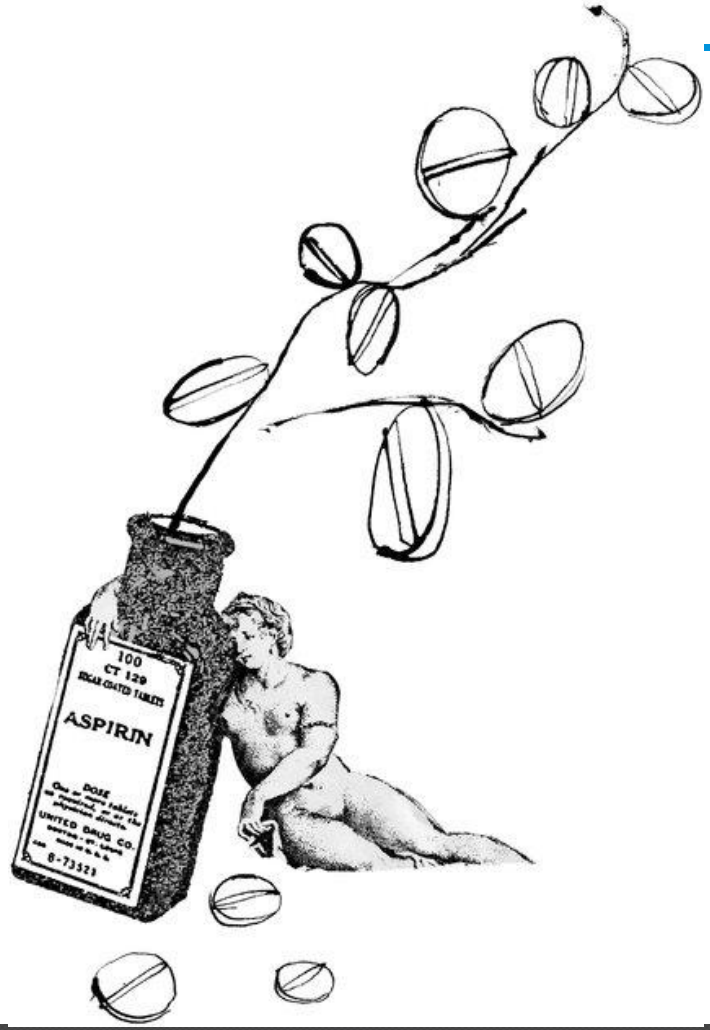
EPIDEMIOLOGY

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

1994+

Aspirin, NSAIDs, sCOX-2i prescriptions

Simvastatin

Prediagnostic HRT

(Opioids, etc.)

Danish Breast Cancer Cooperative Group

1976+

Clinical Registry

Clinical, tumor, treatment data

Breast cancer recurrence

National Prescription Registry (Stats Dk)

Danish National Registry of Patients

1968+

Emigration

Vital status

Danish Civil Registry

1977+

Hospital discharge registry

Comorbid diseases

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

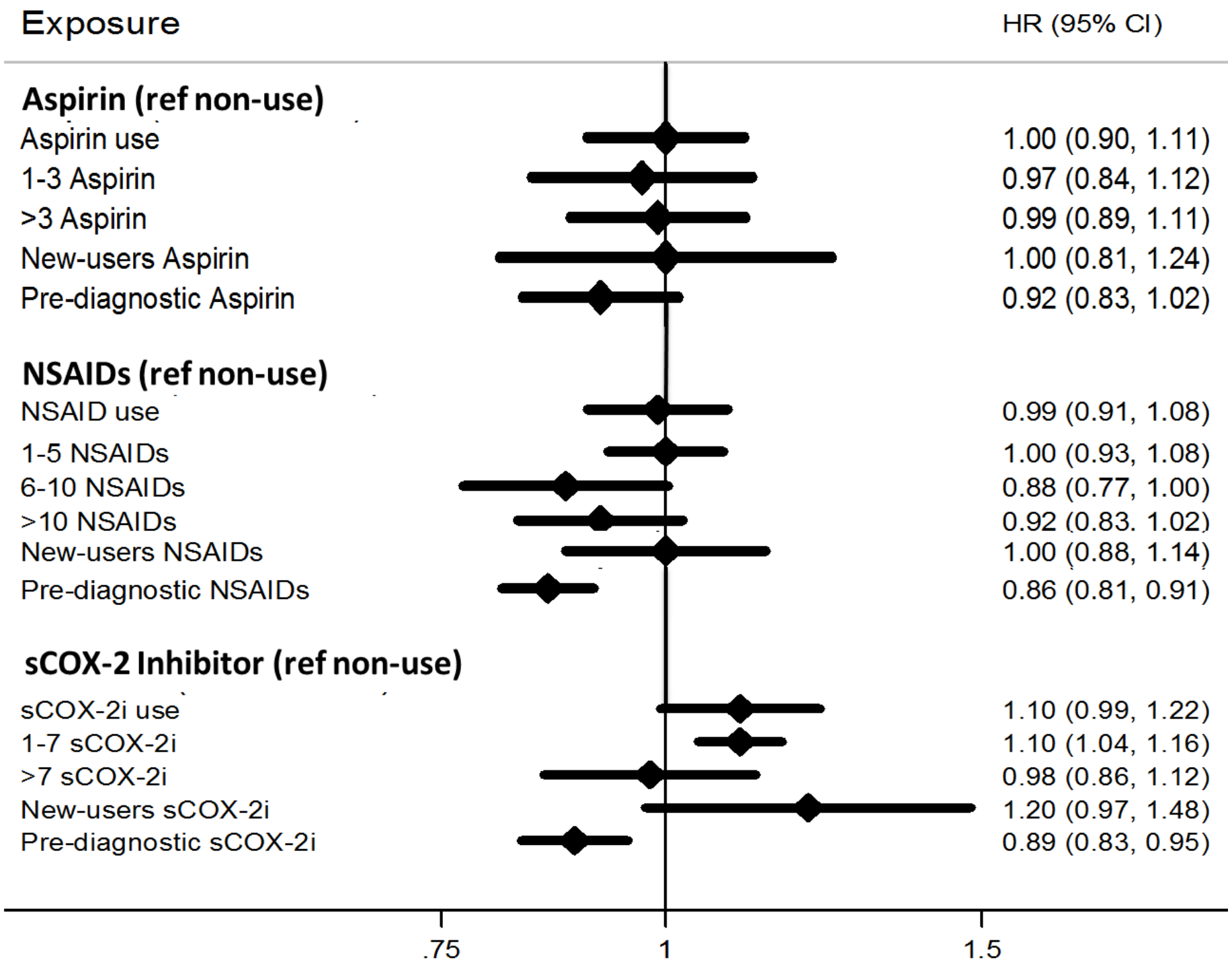
Results

- 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


Exposure
HR (95% CI)
Aspirin (ref non-use)
Aspirin use
1.00 (0.90, 1.11)
1-3 Aspirin
0.97 (0.84, 1.12)
>3 Aspirin
0.99 (0.89, 1.11)
New-users Aspirin
1.00 (0.81, 1.24)
Pre-diagnostic Aspirin
0.92 (0.83, 1.02)
NSAIDs (ref non-use)
NSAID use
0.99 (0.91, 1.08)
1-5 NSAIDs
1.00 (0.93, 1.08)
6-10 NSAIDs
0.88 (0.77, 1.00)
>10 NSAIDs
0.92 (0.83. 1.02)
New-users NSAIDs
1.00 (0.88, 1.14)
Pre-diagnostic NSAIDs
0.86 (0.81, 0.91)
sCOX-2 Inhibitor (ref non-use)
sCOX-2i use
1.10 (0.99, 1.22)
1-7 sCOX-2i
1.10 (1.04, 1.16)
>7 sCOX-2i
0.98 (0.86, 1.12)
New-users sCOX-2i
1.20 (0.97, 1.48)
Pre-diagnostic sCOX-2i
0.89 (0.83, 0.95)
.75
1
1.5

Cancer

Original Article

Opioids and breast cancer recurrence: A Danish population-based cohort study

Deirdre P. Cronin-Fenton PhD[1,*], Uffe Heide-Jørgensen PhD[1], Thomas P. Ahern PhD[2], Timothy L. Lash DSc[1,3], Peer M. Christiansen MD, DMSc[4,5], Bent Ejlertsen MD, PhD[5,6], Per Sjøgren MD, DMSc[7], Henrik Kehlet MD, PhD[8] and Henrik T. Sørensen MD, DMSc[1]

Article first published online: 24 JUL 2015

DOI: 10.1002/cncr.29532

Issue

Cancer

Volume 121, Issue 19, pages 3507–3514, October 1, 2015

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*

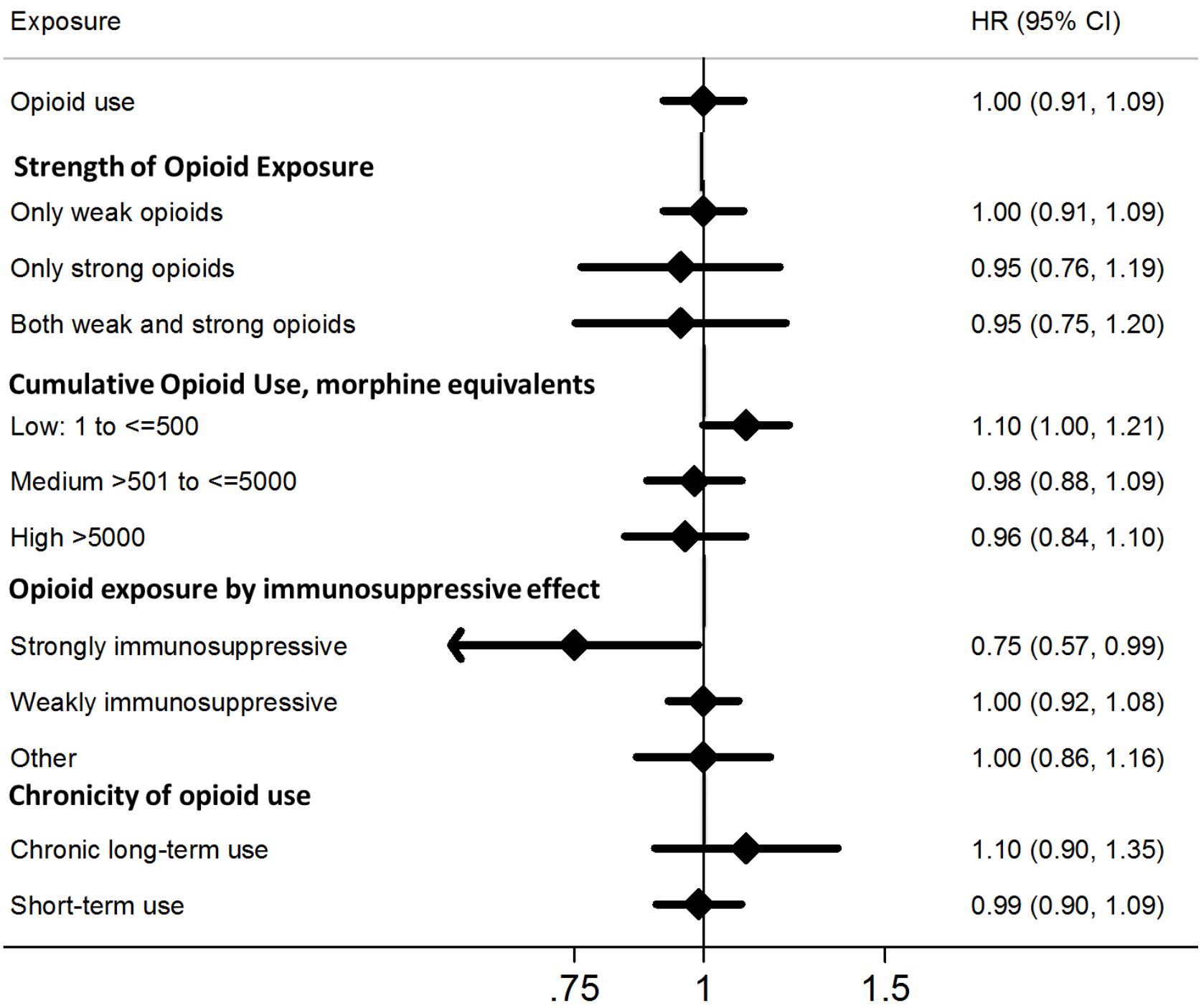
- **Opioid strength:**
  Weak opioids= tramadol, codeine, detropropoxyphene;
  Strong opioids= all others

- **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
HR (95% CI)
Opioid use
1.00 (0.91, 1.09)
Strength of Opioid Exposure
Only weak opioids
1.00 (0.91, 1.09)
Only strong opioids
0.95 (0.76, 1.19)
Both weak and strong opioids
0.95 (0.75, 1.20)
Cumulative Opioid Use, morphine equivalents
Low: 1 to <=500
1.10 (1.00, 1.21)
Medium >501 to <=5000
0.98 (0.88, 1.09)
High >5000
0.96 (0.84, 1.10)
Opioid exposure by immunosuppressive effect
Strongly immunosuppressive
0.75 (0.57, 0.99)
Weakly immunosuppressive
1.00 (0.92, 1.08)
Other
1.00 (0.86, 1.16)
Chronicity of opioid use
Chronic long-term use
1.10 (0.90, 1.35)
Short-term use
0.99 (0.90, 1.09)
.75
1
1.5

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 inhospital or perioperative drug use
- Over-the-counter drug use

Conclusions & Perspectives

- No evidence of an association between post-diagnostic use of opioids, aspirin, NSAIDs, of 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

Acknowledgements

- DBCG
- Danish Cancer Society (R73-A4284-13-S17)
- Aarhus University Research Foundation
- The Lundbeck Foundation (R167-2013-15861)
- Elvira & Rasmus Riisforts Foundation
- Susan G. Komen for Cure (CCR 13264024)
- US NIH (R01CA166825)

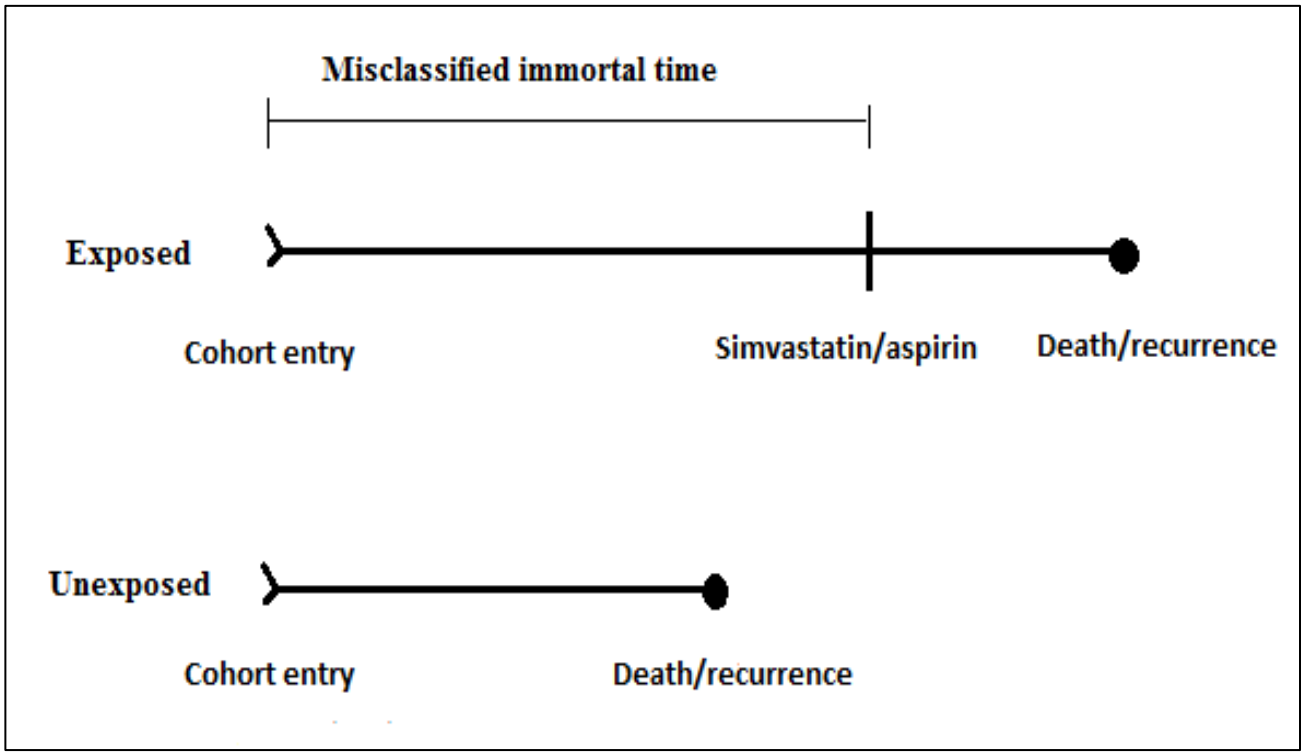


Figure courtesy of Rikke N. Pedersen

Background

EPIDEMIOLOGY

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)*

- 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

Department of Clinical Epidemiology

Pharmaco-epidemiologic research using the DBCG database

Cancer

Original Article

Opioids and breast cancer recurrence: A Danish population-based cohort study

Deirdre P. Cronin-Fenton PhD[1,*], Uffe Heide-Jørgensen PhD[1], Thomas P. Ahern PhD[2], Timothy L. Lash DSc[1,3], Peer M. Christiansen MD, DMSc[4,5], Bent Ejlertsen MD, PhD[5,6], Per Sjøgren MD, DMSc[7], Henrik Kehlet MD, PhD[8] and Henrik T. Sørensen MD, DMSc[1]

Issue

Cancer
Volume 121, Issue 19, pages 3507–3514, October 1, 2015

Article first published online: 24 JUL 2015
DOI: 10.1002/cncr.29532

EPIDEMIOLOGY

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)*