Danish population-based registries in cancer pharmacoepidemiology

Deirdre Cronin Fenton

Cancer Pharmacoepidemiology Meeting
Dublin
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The Epidemiologist’s Dream: Denmark

If the planners of a U.S. study of children’s health could work in an ideal world, it might be Denmark. Epidemiologists there finished enrolling a cohort of 100,000 pregnant women into a mother-and-child research project last September and expect to finish collecting data from the children over the next year. The

in Copenhagen. Each citizen has a personal identification number that can be used to track data in centralized health care records, disease registries, and a population registry. Even centralized school records may be used. “It’s an epidemiologist’s dream,” says Mark Klebanoff of the U.S. National Institute of Child Health and Human Development, who says tracking subjects is one of the costliest aspects of long-term U.S. studies.
The Danish "Cohort"

Lone Frank*

Lone Frank writes from Copenhagen, Denmark.

Denmark has gathered more data on its citizens than any other country. Now scientists are pushing to make this vast array of statistics even more useful.

For years, any woman who got an abortion had to accept more than the loss of her fetus: For some unknown reason, she also faced an elevated risk for breast cancer. At least that was what several small case-control studies had suggested before Mads Melbye, an epidemiologist at the Statens Serum Institute in Copenhagen, undertook the largest effort ever to explore the link. He and his colleagues obtained records on 400,000 women in Denmark's national Abortion Register, then checked how many of the same women were listed in the Danish Cancer Register. Their foray into the two databases led to a surprising result: As they reported in The New England Journal of Medicine in 1997, there appears to be no connection between abortion and breast cancer.

Their success underscores the value of a trove of data the Danish government has accumulated on its citizenry, which today totals about 5 million people. Other Scandinavian countries have created powerful database systems, but Denmark has earned a preeminent reputation for possessing the most complete and interwoven collection of statistics touching on almost every aspect of life. The Danish government has compiled nearly 200 databases, some begun in the 1930s, on everything from medical records to socioeconomic data on jobs and salaries. What makes the databases a plum research tool is the fact that they can all be linked by a 10-digit personal identification number, called the CPR, that follows each Dane from cradle to grave. According to Melbye, "our registers allow for instant, large cohort studies that are impossible in most countries."

But Melbye and other scientists think they can extract even more from this data gold mine. They argue that not enough money is being spent on maintaining and expanding existing databases, and they say that red tape is hampering studies that require correlation of health and demographic data. The problem is that, while they have
The Civil Personal Registration Number

• A unique personal identification number encoding gender and date of birth

• Assigned to all Danish residents at birth or emigration

• Used in all medical contact.......and everywhere else also

• The CPR number

26 03 71 4590

- Birth day
- Birth month
- Birth year
- even=F odd=M
ORIGINAL ARTICLE

The Danish Civil Registration System

A cohort of eight million persons

Carsten Bøcker Pedersen, MSc1, Heine Gøtzsche1, Jørgen Østrup Møller2 and Preben Bo Mortensen, MD, DrMedSc1

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Dan Med Bull 2006;53:441-9

dividual information on CPR-number, gender, date of birth, place of birth, place of residence, citizenship, continuously updated information on vital status, and CPR-number of parents and spouses. The CPR-number is used as a personal identifier in all Danish national registers enabling accurate linkage between all national registers.

In recent years, the CRS has been used as an important research tool in epidemiological research (5), e.g., as regards cancer and psychiatric epidemiology. Linking data from the CRS with information on disease occurrences in the Danish population, it is possible to investigate the association between disease or death in individuals and e.g.: a) disease or death in family members (6, 7), b) place of birth and residence (8), c) immigration (9) and emigration, d) foreign adoptions (10), f) environmental exposures at place of residence (11, 12), g) the geographical distance to environmental exposures (13), h) fertility (14), and i) sibship characteristics (15, 16) using a population-based sample of the Danish population. Other branches of research utilising data recorded in the CRS include clinical research (17) and research based on questionnaires (18).

Individual information included in the CRS will be described with focus on information available on family members, and permanent residence. The quality and completeness of this information will be evaluated and discussed.
Danish Civil Registration System

- Established on April 2, 1968
- Greenland since 1972; no registration for Faroe Islands
- Data registered: CPR-number, name, sex, date & place of birth, residence, citizenship, vital status, CPR-number of parents and spouses + 150 variables
- Updated daily
- The CPR number

- **26 03 71 4590**

  - Birth day
  - Birth month
  - Birth year
  - even=F, odd=M
The CPR number

- Danish Cancer Registry
- Danish National Registry of Patients
- Clinical Databases
- Pathology Archives
- Prescription Databases
- Danish Civil Registry
Cancer Databases in Denmark
Danish Cancer Registry

• Established 1943/compulsory reporting since 1987
• Incident cases of carcinomas, sarcomas, leukaemia, lymphoma, myeloma and mycosis fungoides
• Tumor-like neoplasms and benign tumors: papillomas of urinary tract, benign CNS tumors, carcinomas in-situ at cervical biopsy or smear
• Selected key variables:
  • CPR number
  • Date of diagnosis and method of verification
  • Extent or spread of tumor
  • Treatment up to 4 months after diagnosis
Danish National Patient Registry

- Est. 1977, updated thro’ 2012
- All admissions to public hospitals in Denmark (since 1995 outpatient and emergency visits)
- Selected key variables
  - Patient CPR number
  - Dates of admission and discharge
  - Up to 20 diagnoses (ICD-8 through 1993/ICD-10 thereafter)
  - Hospital-administered medications
  - Hospital and department codes (specialty)
Clinical Cancer Databases

- Urological cancers
- Ovarian cancer
- Colorectal cancer
- Non-melanoma skin cancer
- .......many others
Danish Breast Cancer Cooperative Group Registry

- Est. 1976 to ensure optimal diagnosis and treatment of operable primary breast cancer in Denmark
- >90% of Danish breast cancer cases; >50% on clinical trials
- Detailed information on clinical & treatment characteristics, and follow-up
- Standardized data collection from clinical dept directly to DBCG
- Generalizability of population-based setting with data quality advantages of a clinical trial
Pharmacoepidemiologic research in Denmark
Pharmacoepidemiology studies in Denmark

- The Prescription Registries of the Northern and Central Danish Region (Aarhus University – AUPD)

- The Odense University Pharmacoepidemiological Database (OPED)

- The Danish National Prescription Registry at Statistics Denmark

- Enable compilation of longitudinal drug histories and linking of prescription data to other population-based registries in Denmark
<table>
<thead>
<tr>
<th></th>
<th>National Prescription Database</th>
<th>Aarhus University Prescription Database</th>
</tr>
</thead>
<tbody>
<tr>
<td>Administered by</td>
<td>Statistics Denmark</td>
<td>Department of Clinical Epidemiology, AU</td>
</tr>
<tr>
<td>Population covered</td>
<td>Entire Denmark</td>
<td>Two regions since 1980-90s</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Entire Denmark since 2004</td>
</tr>
<tr>
<td>Period covered</td>
<td>Since 1994</td>
<td>Since 1989-1998-2004 (depending on area)</td>
</tr>
<tr>
<td>Records reimbursed prescriptions</td>
<td>Yes, both generally and</td>
<td>Yes, both generally and</td>
</tr>
<tr>
<td></td>
<td>conditionally reimbursed</td>
<td>conditionally reimbursed</td>
</tr>
<tr>
<td>Non-reimbursed prescriptions</td>
<td>Yes</td>
<td>No (e.g., oral contraceptives, benzodiazepines)</td>
</tr>
<tr>
<td>Hospital drug dispensations</td>
<td>Aggregate only</td>
<td>No</td>
</tr>
<tr>
<td>CPR deleted</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>
Existing data sources for clinical epidemiology: Aarhus University Prescription Database

Abstract: Population-based prescription databases in Nordic countries have become a mainstay of epidemiologic research. Denmark has both national and regional population-based prescription databases. Aarhus University Prescription Database collects data on reimbursed medications dispensed at all community pharmacies of the North Denmark Region and the Central Denmark Region. The regions have a combined population of 1.8 million inhabitants, or one-third of the Danish population. Denmark’s primary health care sector, which includes general practitioners, specialists, and dentists, generates about 96% of the prescription sales,
The population of the new regions ranges from approx. 580,000 in the North Denmark Region to approx. 1,630,000 in The Capital Region of Denmark.

In terms of surface area, The Capital Region of Denmark is the smallest covering 2,561 square kilometres and the Central Denmark Region the largest covering 13,142 square kilometres.

"The Danish regions in brief" (www.regioner.dk).
Prescriptions for selective cyclooxygenase-2 inhibitors, non-selective non-steroidal anti-inflammatory drugs, and risk of breast cancer in a population-based case-control study

Deirdre P Cronin-Fenton\textsuperscript{1*}, Lars Pedersen\textsuperscript{1}, Timothy L Lash\textsuperscript{1,2}, Søren Friis\textsuperscript{3}, John A Baron\textsuperscript{4}, Henrik T Sørensen\textsuperscript{1,2}
Network of Population-based Registries

Population controls (n=81,950)

CIVIL REGISTRY

COUNTY PRESCRIPTION REGISTRY

• NSAIDs,
• sCox-2 inhibitors "newer" & "older"
• Aspirin (low & high dose)
• HRT

CPR#

Danish National Registry of Patients

Breast cancer cases (n=8,195)

Co-morbidities
Drug Exposure

- **Ever** (≥3 pres.) versus **never/rare** use
- **Temporality** of use:
  - Recent users: >3 pres. within 2 yrs of index
  - Former users: ≤3 pres. within 2 yrs of index or ≥3 pres. for all yrs
- **Intensity**: Low, Medium, High
  - # prescriptions / total duration
- **Duration**: Short-term & Long-term
  - # days from “date of 1st to last pres. + duration of last pres.”
Use of glucocorticoids and risk of breast cancer: a Danish population-based case-control study

Gitte Vrelits Sørensen*, Deirdre P Cronin-Fenton, Henrik Toft Sørensen, Sinna Pilgaard Ulrichsen, Lars Pedersen and Timothy L Lash
Antidepressant use and colorectal cancer risk: a Danish population-based case–control study

DP Cronin-Fenton*,†, AH Riis†, TL Lash†,‡, SO Dalton§, S Friis§, D Robertson¶ and HT Sørensen†

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BACKGROUND: Earlier research suggests that use of selective serotonin reuptake inhibitors (SSRIs), but not tricyclic antidepressants (TCAs), reduces the risk of colorectal cancer (CRC).
METHODS: We conducted a population-based case–control study to investigate the association between antidepressant use and CRC risk. Cases were newly diagnosed CRC cases in Denmark from 2002 to 2006. We linked 10 controls matched on age, gender, and county of residence to each case.
Aspirin and Other Nonsteroidal Anti-inflammatory Drugs in Relation to Hodgkin Lymphoma Risk in Northern Denmark

Ellen T. Chang¹,², Deirdre P. Cronin-Fenton³, Søren Friis⁴, Henrik Hjalgrim⁵, Henrik Toft Sørensen³, and Lars Pedersen³

Abstract

There are few known modifiable risk factors for Hodgkin lymphoma, but the recent finding of an inverse association between routine regular-strength aspirin use and Hodgkin lymphoma risk suggests that aspirin may protect against Hodgkin lymphoma development. To further investigate this association using prospectively collected data, we conducted a population-based case-control study in northern Denmark. A total of 478 incident Hodgkin lymphoma cases were identified in nationwide health-care databases from 1991 to 2008. Ten population controls were matched to each case on age, sex, and county using risk-set sampling. Use of aspirin, selective cyclooxygenase-2 inhibitors, and other nonsteroidal anti-inflammatory drugs (NSAIDs) from 1989 to 2007 was ascertained by linkage to a population-based prescription database. Conditional logistic regression was used to estimate odds ratios for associations between medication use and risk of Hodgkin lymphoma. The odds ratio (95% confidence interval) for ever use (>2 prescriptions) compared with never/rare use (≤2 prescriptions) of low-dose aspirin was 0.7 (0.5-1.2). The association with low-dose aspirin was similar across age, sex, smoking, and education strata.
Use of selective serotonin reuptake inhibitors and risk of re-operation due to post-surgical bleeding in breast cancer patients: a Danish population-based cohort study

Rune Gärtnert, Deirdre Cronin-Fenton2, Heidi H Hundborg2, Lars Pedersen2, Timothy L Lash2, Henrik Toft Sørensen2, Niels Kroman1

Abstract

Background: Selective serotonin reuptake inhibitors (SSRI) decrease platelet-function, which suggests that SSRI use may increase the risk of post-surgical bleeding. Few studies have investigated this potential association.

Methods: We conducted a population-based study of the risk of re-operation due to post-surgical bleeding within two weeks of primary surgery among Danish women with primary breast cancer. Patients were categorised according to their use of SSRI: never users, current users (SSRI prescription within 30 days of initial breast cancer surgery), and former users (SSRI prescription more than 30 days before initial breast cancer surgery). We calculated...
Predictors of re-operation due to post-surgical bleeding in breast cancer patients: A Danish population-based cohort study

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bDepartment of Breast Surgery, Aalborg Hospital, Aarhus University Hospital, Denmark
cDepartment of Breast Surgery, Copenhagen University Hospital, Denmark
dDepartment of Medicine, Boston University School of Medicine, USA
eDepartment of Epidemiology & Prevention, Wake Forest School of Medicine, USA

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Available online 17 March 2012

Abstract

Aim: To assess the risk of re-operation due to post-surgical bleeding after initial breast cancer surgery and to identify predictors of re-operation.

Methods: We conducted a population-based study in Denmark. Patients were categorized according to age group, surgery type, and glucocorticoid use before surgery: never, current (0–90 days), and former (>90 days). We calculated the risk of re-operation due to post-surgical bleeding within 14 days after surgery, risk differences, and risk ratios of re-operation associated with age group, surgery type, and glucocorticoid use.

Results: 19,919 women were studied; 508 were re-operated. 3573 of the 19,919 women ever used glucocorticoids. Older age and mastectomy increased the risk of post-surgical bleeding compared with breast conserving surgery and younger age among both ever and never

The Danish National Prescription Database
National Prescription Registry

- Established 1994
- **Individual** outpatient dispensations
- **Aggregate** hospital sales
- Selected key variables
  - Patient CPR number
  - Dispensed drug (ATC code)
  - Date of dispensation
  - Universal Nordic product number, encoding package, formulation, number of pills and DDD
- Administered by Statistics Denmark
Statin Prescriptions and Breast Cancer Recurrence Risk: A Danish Nationwide Prospective Cohort Study

Thomas P. Ahern, Lars Pedersen, Maja Tarp, Deirdre P. Cronin-Fenton, Jens Peter Garne, Rebecca A. Silliman, Henrik Toft Sørensen, Timothy L. Lash

Manuscript received February 8, 2011; revised June 28, 2011; accepted July 5, 2011.

Correspondence to: Thomas P. Ahern, PhD, Channing Laboratory, Department of Medicine, Brigham and Women’s Hospital and Harvard Medical School, 181 Longwood Ave, Rm 355, Boston, MA 02115 (e-mail: nhtpa@channing.harvard.edu).

Background
Accumulating evidence suggests that statins affect diseases other than cardiovascular disease, including cancer, and that these effects may depend on the lipid solubility of specific statins. Though many studies have reported an association between statin use and breast cancer incidence, the relationship between statin use and breast cancer recurrence has not been well studied.

Methods
We conducted a nationwide, population-based prospective cohort study of all female residents in Denmark diagnosed with stage I–III invasive breast carcinoma who were reported to the Danish Breast Cancer Cooperative Group registry between 1996 and 2003 (n = 18769). Women were followed for a median of 6.8 years after diagnosis. Prescriptions for lipophilic and hydrophilic statins were ascertained from the national electronic pharmacy database. Associations between statin prescriptions and breast cancer recurrence were estimated with generalized linear models and Cox proportional hazards regression with adjustment for age and mano-
Aims:

- To measure the association between statin use and the rate of breast cancer recurrence
- To examine this association by
  - Statin solubility (lipophilic versus hydrophilic)
  - Site of breast cancer recurrence
  - Clinical & treatment factors

Hypothesis:

- Use of lipophilic statins, but not hydrophilic statins, is associated with a decreased rate of breast cancer recurrence compared with non-use of statins
Study population & data sources

- Danish population-based cohort study
- Stage I-III breast cancer (n=18,769; n=3,419 recurrences)
- Diagnosis 1996-2003 & registered in DBCG
- Danish National Prescription Database: prescription data
- Danish National Registry of Patients: comorbid diseases
- 10 years of follow-up or through 31/12/2008

Ahern et al., 2011
Definition of statins exposure

Statins exposure:
• >=1 prescription each year after diagnosis

• Lipophilic versus hydrophilic

• Duration (years of exposure) & intensity of use (# of prescriptions)

• Comedications: aspirin, NSAIDs, ACE-inhibitors, vitamin K anticoagulants during follow-up, and pre-diagnosis HRT

Ahern et al., 2011
Statistical Analyses

- Crude and adjusted Cox proportional hazards regression with drug exposure as time-varying covariates lagged by one year
  - Stratified by clinical & treatment factors

- Generalized linear regression models
  - Adjusted risks and risk differences

Ahern et al., 2011
Results

- 3282 statin users
- 2524 (77%) lipophilic statins only
  - 92% simvastatin
- 206 (6.3%) hydrophilic statins only
- 552 (17%) switched categories (excluded)
- 3419 recurrences in 114,006 py
- Median follow-up = 6.8 yrs

Ahern et al., 2011
<table>
<thead>
<tr>
<th>Characteristics of the study cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total n=18,769</td>
</tr>
<tr>
<td>Subjects, n (%)</td>
</tr>
<tr>
<td>Statin Users</td>
</tr>
<tr>
<td>Non-Users</td>
</tr>
<tr>
<td>Menopausal status</td>
</tr>
<tr>
<td>Pre</td>
</tr>
<tr>
<td>Post</td>
</tr>
<tr>
<td>514 (16)</td>
</tr>
<tr>
<td>5,077 (33)</td>
</tr>
<tr>
<td>2,768 (84)</td>
</tr>
<tr>
<td>10,407 (67)</td>
</tr>
<tr>
<td>UICC Stage</td>
</tr>
<tr>
<td>I</td>
</tr>
<tr>
<td>II</td>
</tr>
<tr>
<td>III</td>
</tr>
<tr>
<td>1,352 (41)</td>
</tr>
<tr>
<td>1,481 (45)</td>
</tr>
<tr>
<td>448 (14)</td>
</tr>
<tr>
<td>5,836 (38)</td>
</tr>
<tr>
<td>6,663 (43)</td>
</tr>
<tr>
<td>2,982 (19)</td>
</tr>
<tr>
<td>Histologic grade</td>
</tr>
<tr>
<td>Low</td>
</tr>
<tr>
<td>Moderate</td>
</tr>
<tr>
<td>High</td>
</tr>
<tr>
<td>975 (36)</td>
</tr>
<tr>
<td>1,195 (44)</td>
</tr>
<tr>
<td>539 (20)</td>
</tr>
<tr>
<td>4,109 (33)</td>
</tr>
<tr>
<td>5,414 (43)</td>
</tr>
<tr>
<td>3,088 (24)</td>
</tr>
<tr>
<td>ER/endocrine therapy</td>
</tr>
<tr>
<td>ER+/ET+</td>
</tr>
<tr>
<td>ER-/ET-</td>
</tr>
<tr>
<td>ER+/ET-</td>
</tr>
<tr>
<td>ER-/ET+</td>
</tr>
<tr>
<td>1,649 (52)</td>
</tr>
<tr>
<td>555 (17)</td>
</tr>
<tr>
<td>964 (30)</td>
</tr>
<tr>
<td>8 (0.3)</td>
</tr>
<tr>
<td>6,654 (45)</td>
</tr>
<tr>
<td>3,240 (22)</td>
</tr>
<tr>
<td>4,933 (33)</td>
</tr>
<tr>
<td>28 (0.2)</td>
</tr>
</tbody>
</table>
Statin prescription & breast cancer recurrence

Exclusive Simvastatin:
- Adj. 10-year risk difference = -0.10 (95% CI= -0.11, -0.08)
- Adj. HR = 0.70 (95% CI= 0.57, 0.86)

Hydrophilic statins:
- Adj. 10-year risk difference = 0.05 (95%CI= -0.01, 0.11)
- Adj. HR = 1.2 (95% CI = 0.79, 1.7)
### Breast cancer recurrences by statin use

<table>
<thead>
<tr>
<th></th>
<th>Recurrences/ person-years</th>
<th>Unadjusted Hazard Ratio (95% CI)</th>
<th>Adjusted Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ten-year recurrence:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never prescribed a statin</td>
<td>3,170/88,384</td>
<td>1. ref</td>
<td>1. ref</td>
</tr>
<tr>
<td>Any statin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Only hydrophilic</td>
<td>249/12,137</td>
<td>0.87 (0.75, 1.0)</td>
<td>0.83 (0.70, 0.98)</td>
</tr>
<tr>
<td>Only lipophilic</td>
<td>39/951</td>
<td>1.2 (0.83, 1.7)</td>
<td>1.2 (0.79, 1.7)</td>
</tr>
<tr>
<td>Only simvastatin</td>
<td>182/8,263</td>
<td>0.86 (0.73, 1.0)</td>
<td>0.73 (0.60, 0.89)</td>
</tr>
<tr>
<td></td>
<td>166/7,889</td>
<td>0.83 (0.69, 0.99)</td>
<td>0.70 (0.57, 0.86)</td>
</tr>
<tr>
<td>Only hydrophilic</td>
<td>39/951</td>
<td>1. ref</td>
<td>1. ref</td>
</tr>
<tr>
<td>Only lipophilic</td>
<td>182/8,263</td>
<td>0.69 (0.47, 1.0)</td>
<td>0.59 (0.39, 0.91)</td>
</tr>
<tr>
<td>Only simvastatin</td>
<td>166/7,889</td>
<td>0.65 (0.43, 0.96)</td>
<td>0.55 (0.35, 0.85)</td>
</tr>
</tbody>
</table>
Simvastatin prescription versus never prescription

<table>
<thead>
<tr>
<th>Stratified models</th>
<th>Recurrences, n (%)</th>
<th>Adjusted Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estrogen receptor status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>862 (27)</td>
<td>0.75 (0.47, 1.2)</td>
</tr>
<tr>
<td>Positive</td>
<td>2,309 (73)</td>
<td>0.69 (0.55, 0.88)</td>
</tr>
<tr>
<td>Histologic grade</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>608 (22)</td>
<td>0.59 (0.39, 0.89)</td>
</tr>
<tr>
<td>Moderate</td>
<td>1,245 (45)</td>
<td>0.75 (0.55, 1.0)</td>
</tr>
<tr>
<td>High</td>
<td>928 (33)</td>
<td>0.76 (0.51, 1.1)</td>
</tr>
<tr>
<td>Type of primary therapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mastectomy, no RT</td>
<td>1,466 (65)</td>
<td>0.72 (0.54, 0.96)</td>
</tr>
<tr>
<td>Breast-conserving surgery, with RT</td>
<td>785 (35)</td>
<td>0.68 (0.46, 1.0)</td>
</tr>
</tbody>
</table>
## Simvastatin prescription versus never prescription

<table>
<thead>
<tr>
<th>Recurrence site-specific models</th>
<th>Recurrences, n (%)</th>
<th>Adjusted Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone</td>
<td>1,087 (33)</td>
<td>0.91 (0.65, 1.3)</td>
</tr>
<tr>
<td>Contralateral breast</td>
<td>520 (16)</td>
<td>0.54 (0.33, 0.90)</td>
</tr>
<tr>
<td>Ipsilateral breast</td>
<td>550 (17)</td>
<td>0.57 (0.32, 1.0)</td>
</tr>
<tr>
<td>Lymph node</td>
<td>527 (16)</td>
<td>0.56 (0.31, 1.0)</td>
</tr>
<tr>
<td>Lungs and pleura</td>
<td>294 (8.8)</td>
<td>0.67 (0.34, 1.3)</td>
</tr>
<tr>
<td>Liver</td>
<td>203 (6.1)</td>
<td>0.96 (0.40, 2.3)</td>
</tr>
<tr>
<td>Central nervous system</td>
<td>66 (2.0)</td>
<td>0.60 (0.08, 4.7)</td>
</tr>
<tr>
<td>All other sites</td>
<td>89 (2.7)</td>
<td>n/a</td>
</tr>
</tbody>
</table>
Strengths

• Large size & prospective data
• High quality registry data
  • DBCG
  • National Registry of Medicinal Products
  • Danish National Registry of Patients
• Information on site of recurrence & clinical factors
• Lipophilic versus hydrophilic statins
Limitations

- Prescription compliance
  - Prescriptions retrieved at pharmacy

- No information on body mass index

- Confounding by indication
  - Hypercholesterolemia?
Conclusions

• Lipophilic statins, but not hydrophilic statins, are associated with a decreased risk of breast cancer recurrence
Statins & Breast Cancer Recurrence

<table>
<thead>
<tr>
<th>Citation</th>
<th>RR (95% CI)</th>
<th>% Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kwan et al., 2008</td>
<td>0.67 (0.39, 1.14)</td>
<td>8.28</td>
</tr>
<tr>
<td>Chae et al., 2011</td>
<td>0.40 (0.24, 0.67)</td>
<td>8.90</td>
</tr>
<tr>
<td>Ahern et al., 2011</td>
<td>0.83 (0.70, 0.98)</td>
<td>82.82</td>
</tr>
<tr>
<td>Overall</td>
<td>0.76 (0.66, 0.89)</td>
<td>100.00</td>
</tr>
</tbody>
</table>
Implications of the “statins” paper......

- Statins & recurrence in other cancers?

- Clinical trial of simvastatin & breast cancer recurrence
  - DBCG

**DBCG**
*Danish Breast Cancer Cooperative Group*
ORIGINAL ARTICLE

Breast cancer recurrence risk related to concurrent use of SSRI antidepressants and tamoxifen

TIMOTHY L. LASH¹,²,³, DEIRDRE CRONIN-FENTON¹, THOMAS P. AHERN², CAROL L. ROSENBERG³, KATHRYN L. LUNETTA⁴, REBECCA A. SILLIMAN³, STEPHEN HAMILTON-DUTOIT⁵, JENS PETER GARNE⁶,⁷, MARIANNE EWERTZ⁷,⁸, HENRIK TOFT SØRENSEN¹,²,⁷ & LARS PEDERSEN¹

¹Department of Clinical Epidemiology, Aarhus University Hospital, Denmark, ²Department of Epidemiology, Boston University School of Public Health, USA, ³Department of Medicine, Boston University School of Medicine, USA, ⁴Department of Biostatistics, Boston University School of Public Health, USA, ⁵Institute of Pathology.
Use of β-Blockers, Angiotensin-Converting Enzyme Inhibitors, Angiotensin II Receptor Blockers, and Risk of Breast Cancer Recurrence: A Danish Nationwide Prospective Cohort Study

Gitte Vrelits Sørensen, Patricia A. Ganz, Steven W. Cole, Lars A. Pedersen, Henrik Toft Sørensen, Deirdre P. Cronin-Fenton, Jens Peter Garne, Peer M. Christiansen, Timothy L. Lash, and Thomas P. Ahern

ABSTRACT

Purpose
To estimate associations between use of β-blockers, angiotensin-converting enzyme (ACE) inhibitors, or angiotensin receptor blockers (ARBs) and breast cancer recurrence in a large Danish cohort.

Patients and Methods
We enrolled 18,733 women diagnosed with nonmetastatic breast cancer between 1996 and 2003. Patient, treatment, and 10-year recurrence data were ascertained from the Danish Breast Cancer Cooperative Group registry. Prescription and medical histories were ascertained by linkage to the National Prescription Registry and Registry of Patients, respectively. β-Blocker exposure was defined in aggregate and according to solubility, receptor selectivity, and individual drugs. ACE inhibitor and ARB exposures were defined in aggregate. Recurrence associations were estimated with multivariable Cox regression models in which time-varying drug exposures were lagged by 1 year.
Null Results in Brief

No Increase in Breast Cancer Recurrence with Concurrent Use of Tamoxifen and Some CYP2D6-Inhibiting Medications

Thomas P. Ahem, Lars Pedersen, Deirdre P. Cronin-Fenton, Henrik Toft Sørensen, and Timothy L. Lash

Department of Epidemiology, Boston University School of Public Health, Boston, Massachusetts and Department of Clinical Epidemiology, Aarhus University Hospital, Aarhus, Denmark

Abstract

Tamoxifen reduces recurrence risk among women treated for estrogen receptor-positive breast cancer. Its effectiveness partly depends on metabolic activation via cytochrome P450 2D6 (CYP2D6). Some medications compromise CYP2D6 activity and may lower plasma concentrations of active tamoxifen metabolites. We studied the association between concurrent use of tamoxifen and CYP2D6-inhibiting medications and breast cancer recurrence among Danish women diagnosed with early-stage, estrogen receptor-positive breast cancer. Using the Danish Breast Cancer Cooperative Group Registry, we identified 366 cases with local or distant breast cancer recurrence and 366 matched breast cancer controls. We ascertained concurrent prescription of CYP2D6-inhibiting medications during tamoxifen treatment by linking to the national prescription database covering all Danish pharmacies. We computed the breast cancer recurrence odds ratio (OR) and 95% confidence interval for each medication. The pooled recurrence OR was null (OR, 1.0; 95% confidence interval, 0.8-1.3); recurrence ORs for individual drugs ranged from 0.3 to 3.4. The individual ORs followed the pattern expected under a null-centered Gaussian distribution. Null associations were apparent for all drugs after empirical Bayes adjustment for multiple comparisons. Together, these results provide evidence for a null association between drug-compromised CYP2D6 activity and breast cancer recurrence among tamoxifen-treated women. (Cancer Epidemiol Biomarkers Prev 2009;18(9):2562-4)
CYP2D6 Inhibition and Breast Cancer Recurrence in a Population-Based Study in Denmark

Timothy L. Lash, Deirdre Cronin-Fenton, Thomas P. Ahern, Carol L. Rosenberg, Kathryn L. Lunetta, Rebecca A. Silliman, Jens Peter Garne, Henrik Toft Sørensen, Ylva Hellberg, Mariann Christensen, Lars Pedersen, Stephen Hamilton-Dutoit

Manuscript received August 13, 2010; revised December 31, 2010; accepted January 5, 2011.

Correspondence to: Timothy L. Lash, DSc, MPH, Department of Clinical Epidemiology, Aarhus University Hospital, Olof Palmes Alle 43, 8200 Aarhus N, Denmark (e-mail: tl@deo.au.dk).

Background
Cytochrome P450 2D6 (CYP2D6) inhibition reduces the concentration of 4-hydroxylated tamoxifen metabolites, but the clinical relevance remains uncertain.

Methods
We conducted a large case–control study nested in the population of 11,251 women aged 35–69 years at diagnosis of stage I–III breast cancer between 1985 and 2001 on Denmark’s Jutland Peninsula and registered with the Danish Breast Cancer Cooperative Group. We identified 541 recurrent or contralateral breast cancers among women with estrogen receptor–positive (ER+) disease treated with tamoxifen for at least 1 year and 300 cancers in women with ER-negative (ER−) disease never treated with tamoxifen. We matched one control subject per case patient on ER status, menopausal status, stage, calendar time, and county, genotyped the CYP2D6*4 allele to assess genetic inhibition, and ascertained prescription history to assess drug–drug inhibition. We estimated the odds ratio (OR), associating CYP2D6 inhibition with breast cancer recurrence and adjusted for potential confounding with logistic regression. To address bias from incomplete information on CYP2D6 function, we used Monte Carlo simulation to complete a record-level probabilistic bias analysis. All statistical tests were two-sided.
The Department of Clinical Epidemiology

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Information on Danish Registry Sources

"Use of Medical Databases in Clinical Epidemiology"
Sorensen, Christensen, Schlosser, Pedersen (Eds)
See: http://kea.au.dk/en/research/

Clinical Epidemiology *free online journal*
Special Danish registries edition: 2010
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- Danish Medical Research Council
- US National Cancer Institute
Mange tak!