Department of Clinical Epidemiology

Danish population-based registries in cancer pharmacoepidemiology

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Cancer Pharmacoepidemiology Meeting

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Aarhus University Hospital

AARHUS UNIVERSITY

www.kea.au.dk

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.

Science 31 March 2000:
Vol. 287 no. 5462 pp. 2398-2399
DOI: 10.1126/science.287.5462.2398

The Danish "Cohort"

NEWS FOCUS

EPIDEMIOLOGY

When an Entire Country Is a 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

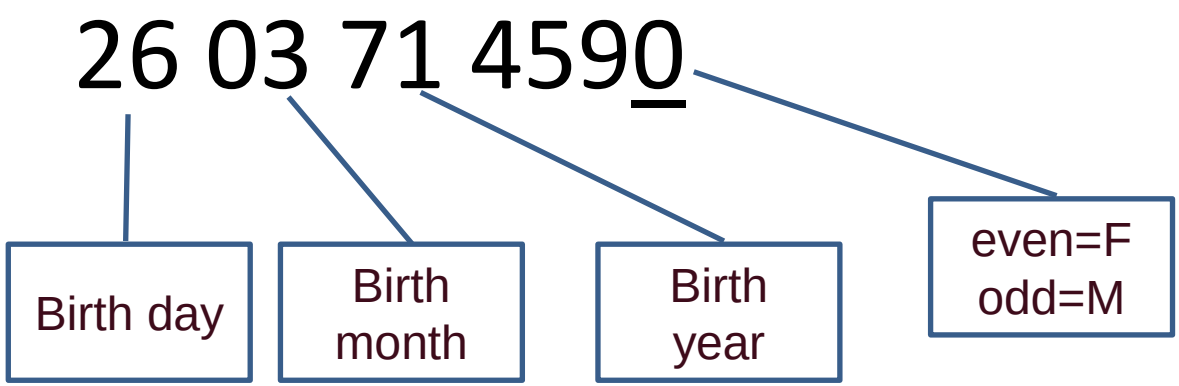
For years, any woman who got an abortion had to accept more than the loss of her fetus: For some unknown reason, she also faced an elevated risk for breast cancer. At least that was what several small case-control studies had suggested before Mads Melbye, an epidemiologist at the Statens Serum Institute 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**



ORIGINAL ARTICLE

The Danish Civil Registration System

A cohort of eight million persons

Carsten Bøcker Pedersen, MSc[1], Heine Gøtzsche[1], Jørgen Østrup Møller[2] and Preben Bo Mortensen, MD, DrMedSc[1]

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Correspondence: Carsten Bøcker Pedersen, National Centre for Register-based Research, University of Aarhus, Taasingegade 1, 8000 Aarhus C, Denmark,

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Dan Med Bull 2006;53:441-9

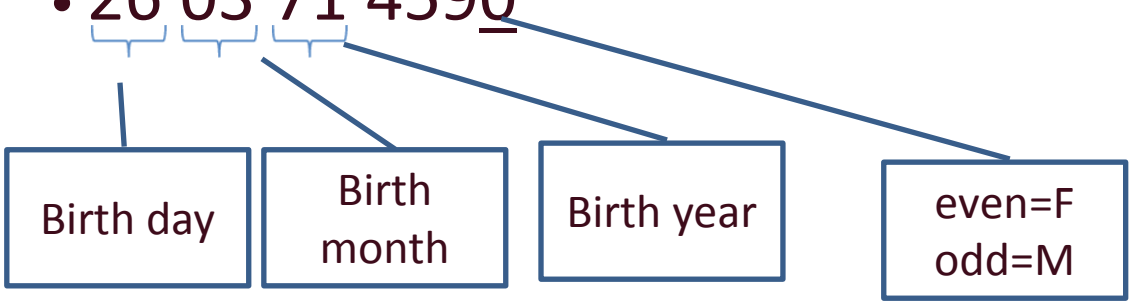
dividual information on CPR-number, gender, date of birth, place of birth, place of residence, citizenship, continuously updated information on vital status, and CPR-number of parents and spouses. The CPR-number is used as a personal identifier in all Danish national registers enabling accurate linkage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

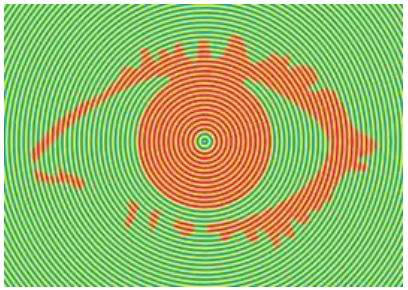
Individual information included in the CRS will be described with focus on information available on family members, and permanent residence. The quality and completeness of this information will be evaluated and discussed.

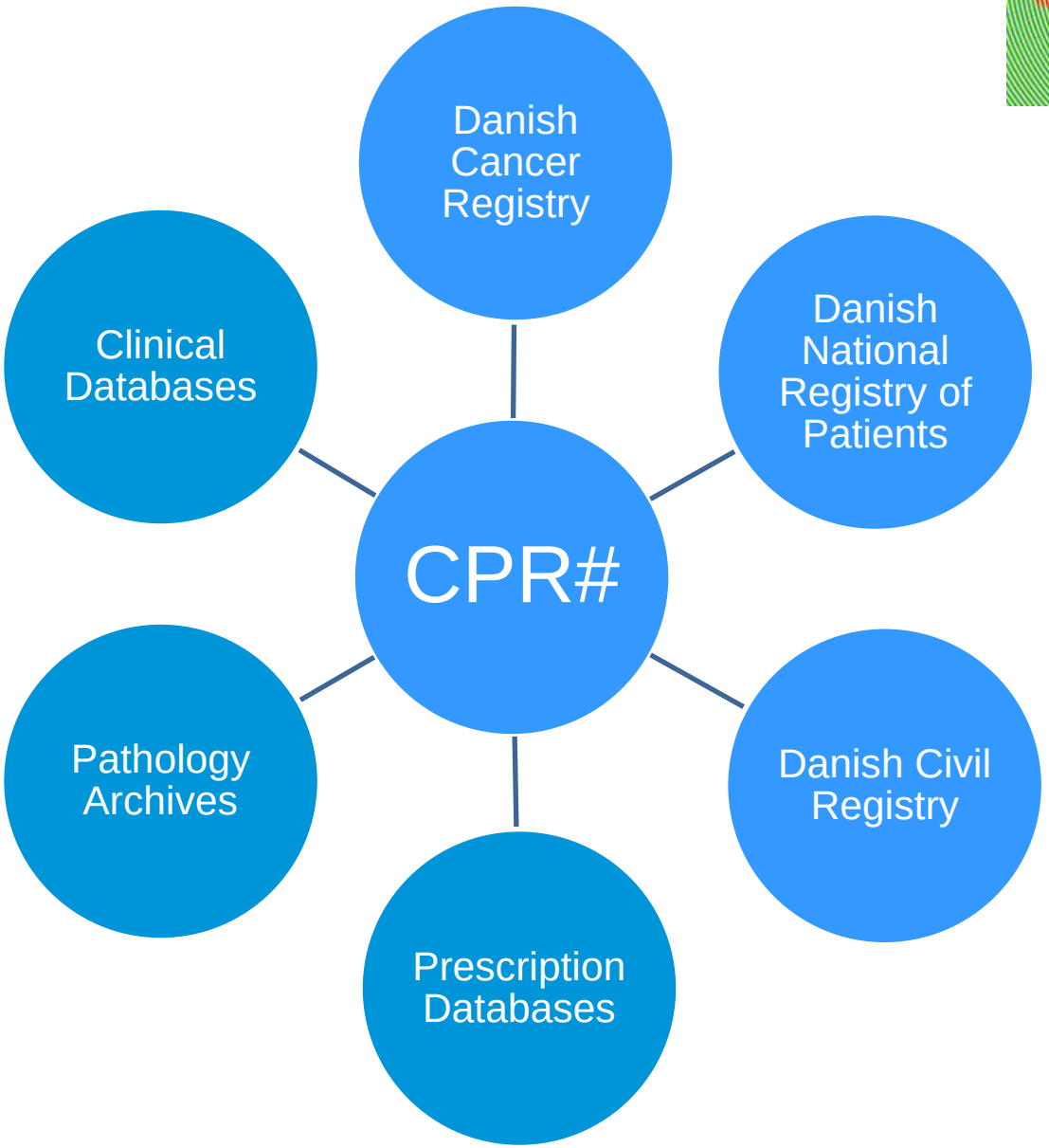
Danish Civil Registration System

- 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



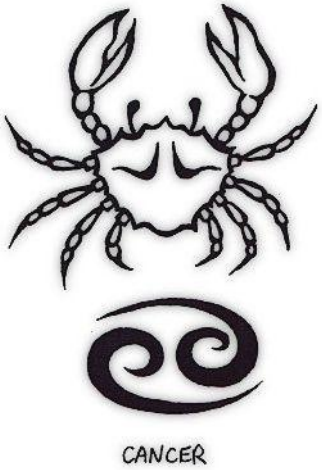
The CPR number





Cancer Databases in Denmark

Kræftens Bekæmpelse



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

DBCG | Danish Breast Cancer Cooperative Group

- 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

COMPARISON OF NATIONAL AND AUPD PRESCRIPTION DATA

	National Prescription Database	Aarhus University Prescription Database
Administered by	Statistics Denmark	Department of Clinical Epidemiology, AU
Population covered	Entire Denmark	Two regions since 1980-90s Entire Denmark since 2004
Period covered	Since 1994	Since 1989-1998-2004 (depending on area)
Records reimbursed prescriptions	Yes, both generally and conditionally reimbursed	Yes, both generally and conditionally reimbursed
Non-reimbursed prescriptions	Yes	No (e.g., oral contraceptives, benzodiazepines)
Hospital drug dispensations	Aggregate only	No
CPR deleted	Yes	No

Clinical Epidemiology

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METHODOLOGY

Existing data sources for clinical epidemiology: Aarhus University Prescription Database

This article was published in the following Dove Press journal:
Clinical Epidemiology
1 December 2010
Number of times this article has been viewed

Vera Ehrenstein
Sussie Antonsen
Lars Pedersen

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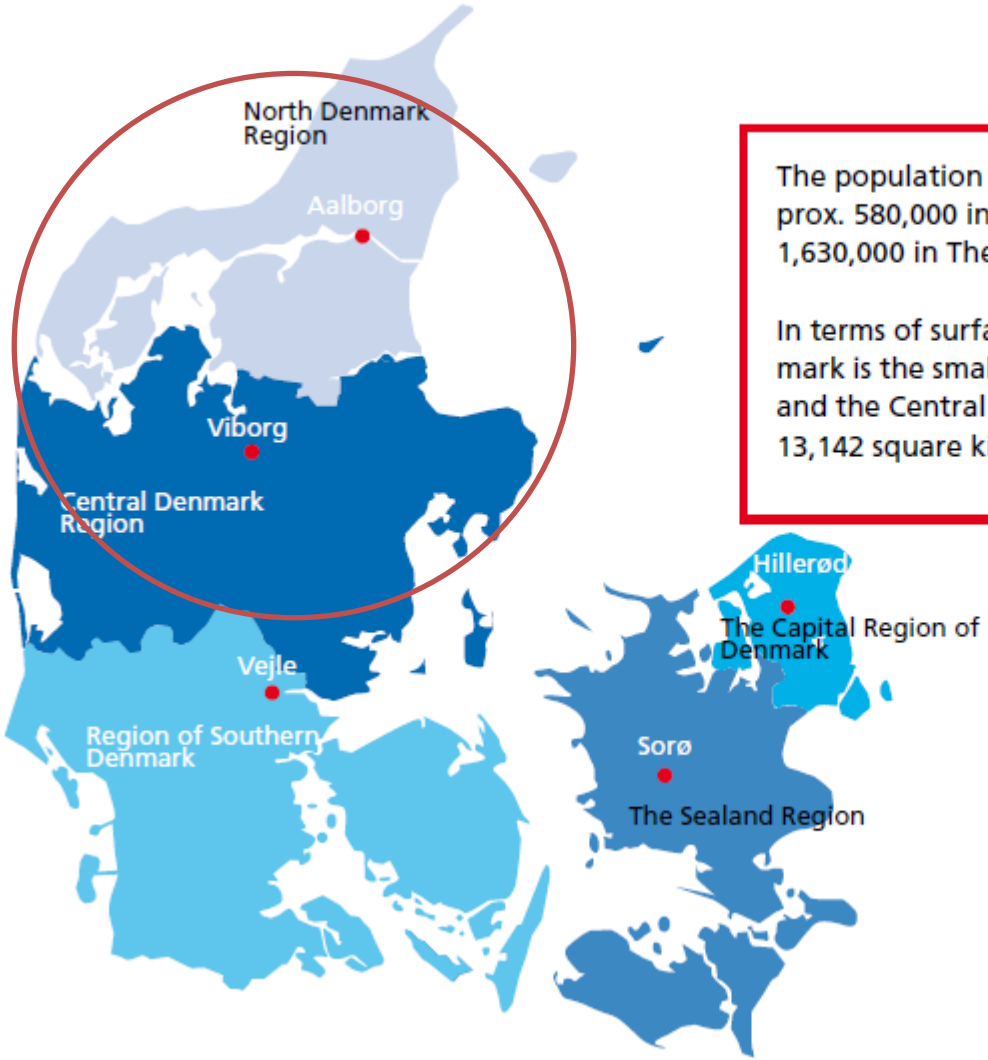
Abstract: Population-based prescription databases in Nordic countries have become a mainstay of epidemiologic research. Denmark has both national and regional population-based prescription databases. Aarhus University Prescription Database collects data on reimbursed medications dispensed at all community 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).

Cronin-Fenton *et al. Breast Cancer Research* 2010, **12**:R15
http://breast-cancer-research.com/content/12/2/R15

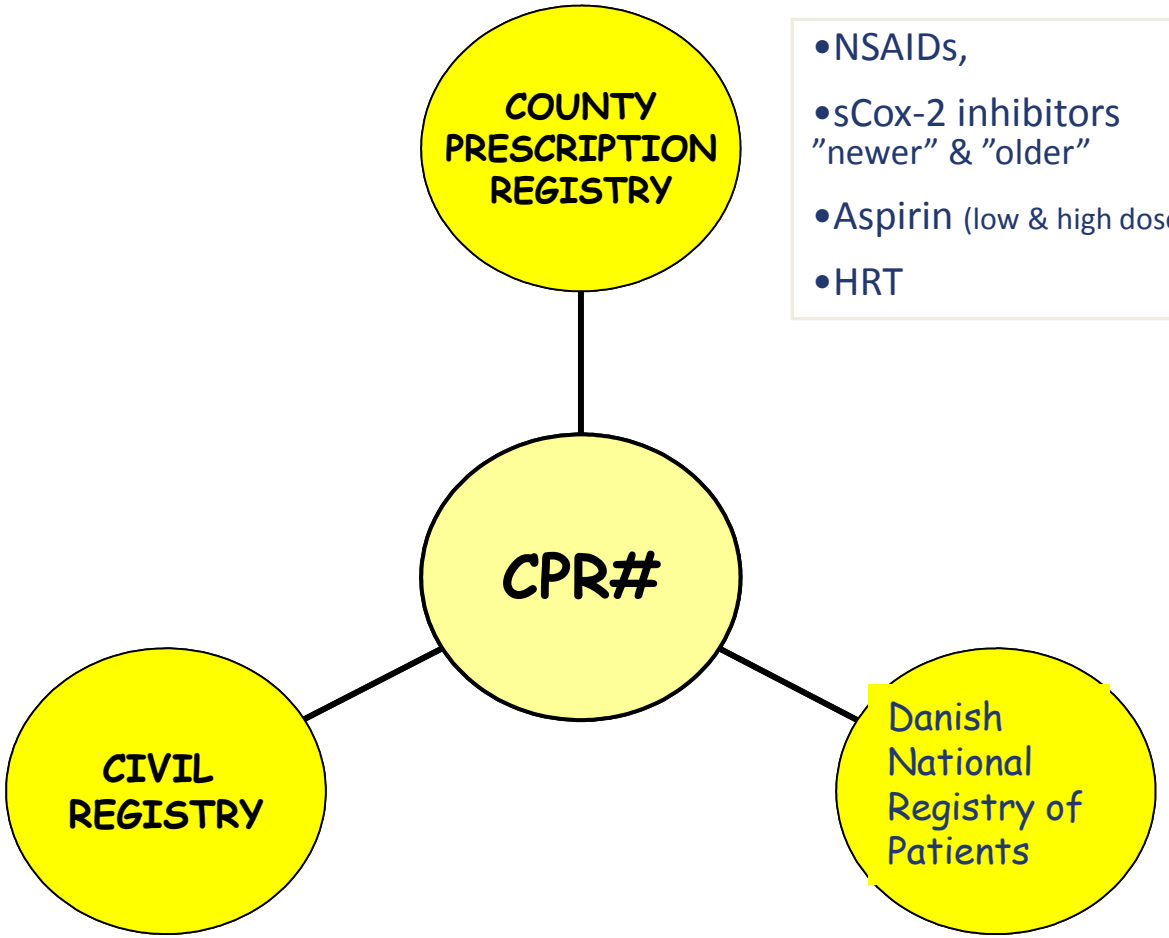
Breast Cancer RESEARCH

RESEARCH ARTICLE Open Access

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[1*], Lars Pedersen[1], Timothy L Lash[1,2], Søren Friis[3], John A Baron[4], Henrik T Sørensen[1,2]

Network of Population-based Registries



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

Population controls (n=81,950)

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."

Sørensen *et al. Breast Cancer Research* 2012, **14**:R21
http://breast-cancer-research.com/content/14/1/R21

Breast Cancer RESEARCH

RESEARCH ARTICLE Open Access

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

British Journal of Cancer (2011) 104, 188 – 192
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www.bjcancer.com

Antidepressant use and colorectal cancer risk: a Danish population-based case–control study

DP Cronin-Fenton*[,1], AH Riis[1], TL Lash[1,2], SO Dalton[3], S Friis[3], D Robertson[4] and HT Sørensen[1]

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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

Cancer Epidemiology, Biomarkers & Prevention

Research Article

Aspirin and Other Nonsteroidal Anti-inflammatory Drugs in Relation to Hodgkin Lymphoma Risk in Northern Denmark

Ellen T. Chang[1,2], Deirdre P. Cronin-Fenton[3], Søren Friis[4], Henrik Hjalgrim[5], Henrik Toft Sørensen[3], and Lars Pedersen[3]

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

Gärtner et al. BMC Surgery 2010, 10:3
http://www.biomedcentral.com/1471-2482/10/3

BMC Surgery

RESEARCH ARTICLE Open Access

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 Gärtner[1], Deirdre Cronin-Fenton[2], Heidi H Hundborg[2,3], Lars Pedersen[2], Timothy L Lash[2,4], Henrik Toft Sørensen[2*], Niels Kroman[1]

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

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EJSO 38 (2012) 407–412

EJSO
the Journal of Cancer Surgery

www.ejso.com

Predictors of re-operation due to post-surgical bleeding in breast cancer patients: A Danish population-based cohort study

L. Winther Lietzen [a,*], D. Cronin-Fenton [a], J.P. Garne [b], N. Kroman [c], R. Silliman [d], T.L. Lash [a,d,e]

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[d] Department of Medicine, Boston University School of Medicine, USA
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Accepted 27 February 2012
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.

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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 meno-

Statins & Breast Cancer Recurrence

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

Characteristics of the study cohort

Total n=18,769	Subjects, n (%)	
	Statin Users	Non-Users
Menopausal status		
Pre	514 (16)	5,077 (33)
Post	2,768 (84)	10,407 (67)
UICC Stage		
I	1,352 (41)	5,836 (38)
II	1,481 (45)	6,663 (43)
III	448 (14)	2,982 (19)
Histologic grade		
Low	975 (36)	4,109 (33)
Moderate	1,195 (44)	5,414 (43)
High	539 (20)	3,088 (24)
ER/endocrine therapy		
ER+/ET+	1,649 (52)	6,654 (45)
ER-/ET-	555 (17)	3,240 (22)
ER+/ET-	964 (30)	4,933 (33)
ER-/ET+	8 (0.3)	28 (0.2)

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)

Ahern *et al.*, 2011

Statin prescription & ten-year breast cancer recurrence

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

Simvastatin prescription versus never prescription

Stratified models	Recurrences, n (%)		Adjusted Hazard Ratio (95% CI)
Estrogen receptor status			
Negative	862	(27)	0.75 (0.47, 1.2)
Positive	2,309	(73)	0.69 (0.55, 0.88)
Histologic grade			
Low	608	(22)	0.59 (0.39, 0.89)
Moderate	1,245	(45)	0.75 (0.55, 1.0)
High	928	(33)	0.76 (0.51, 1.1)
Type of primary therapy			
Mastectomy, no RT	1,466	(65)	0.72 (0.54, 0.96)
Breast-conserving surgery, with RT	785	(35)	0.68 (0.46, 1.0)

Simvastatin prescription versus never prescription

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

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

Ahern *et al.*, 2011

Limitations

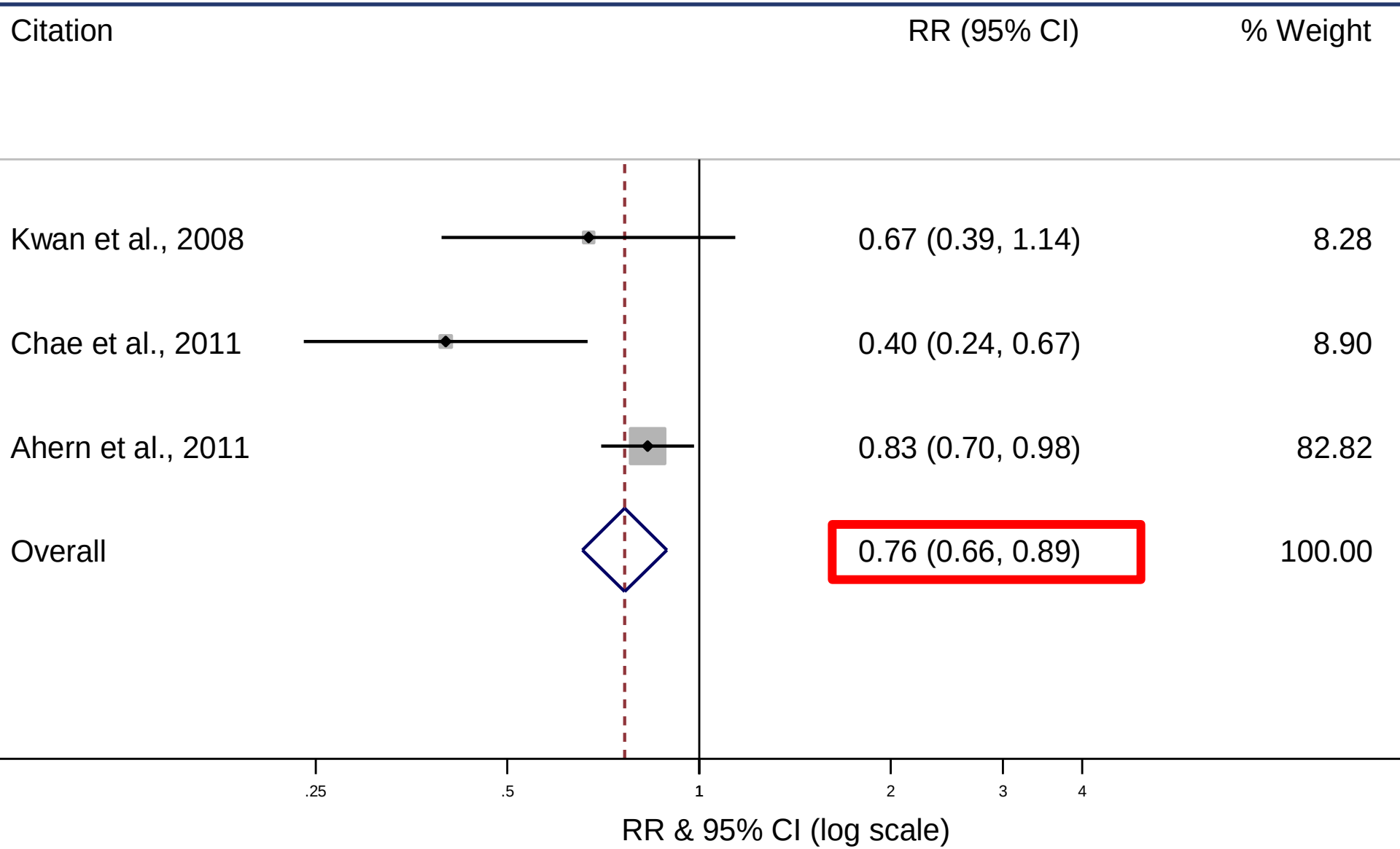
- Prescription compliance
  - Prescriptions retrieved at pharmacy
- No information on bodymass index
- Confounding by indication
  - Hypercholesterolemia?

Ahern *et al.*, 2011

Conclusions

- Lipophilic statins, but not hydrophilic statins, are associated with a decreased risk of breast cancer recurrence

Statins & Breast Cancer Recurrence



Implications of the "statins" paper……

- Statins & recurrence in other cancers?

- Clinical trial of simvastatin & breast cancer recurrence
  - DBCG

DBCG | Danish Breast Cancer Cooperative Group

Acta Oncologica, 2010; 49: 305–312

informa
healthcare

ORIGINAL ARTICLE

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

TIMOTHY L. LASH[1,2,3], DEIRDRE CRONIN-FENTON[1], THOMAS P. AHERN[2], CAROL L. ROSENBERG[3], KATHRYN L. LUNETTA[4], REBECCA A. SILLIMAN[3], STEPHEN HAMILTON-DUTOIT[5], JENS PETER GARNE[6,7], MARIANNE EWERTZ[7,8], HENRIK TOFT SØRENSEN[1,2,7] & LARS PEDERSEN[1]

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JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

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

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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

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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

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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.

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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/

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