BRUG AF ANDEN RECEPTPLIGTIG MEDICIN

DEIRDRE CRONIN FENTON

DBCG 40-års Jubilæumsmøde
18-19 januar 2018

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UNIVERSITY
DEPARTMENT OF CLINICAL MEDICINE

ACTA ONCOLOGICA, 2017
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ORIGINAL ARTICLE

Concurrent new drug prescriptions and prognosis of early breast cancer: studies using the Danish Breast Cancer Group clinical database

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Article
Opioids and Breast Cancer Recurrence: A Dan
Population-Based Cohort Study
Deirdre P. Cronin-Fenton, PhD[1]; Uffe Heide-Jørgensen, PhD[1]; Thomas P. Ahern, PhD[2]; Timothy
Peer M. Christiansen, MD, DMSc[4,5]; Bent Ejlertsen, MD, PhD[5,6]; Per Sjøgren, MD, DMSc[7]; Henrik
and Henrik T. Sørensen, MD, DMSc[1]
Biggar et al. Breast Cancer Research 2013, 15:R13
http://breast-cancer-research.com/content/15/1/R13
Breast Cancer RESEARCH
RESEARCH ARTICLE
Open Access
Breast cancer in women using digoxin: tumor characteristics and relaps
Robert J Biggar[1,2*], Elisabeth W Andersen[1], Niels Kroman
Abstract
Use of β-Blockers, Angiotensin-Converting Enzy
Inhibitors, Angiotensin II Receptor Blockers, and
Breast Cancer Recurrence: A Danish Nationwide
Prospective Cohort Study
Vrelits Sørensen, Patricia A. Ganz, Steven W. Cole, Lars A. Pedersen, Henrik Toft Sørens
P. Cronin-Fenton, Jens Peter Garne, Peer M. Christiansen, Timothy L. Lash, and Thon
Low-dose Aspirin, Nonsteroidal Anti-inflammat
Selective COX-2 Inhibitors and Bre
Deirdre P. Cronin-Fenton
Tamoxifen's protection against breast cancer recurrence is not reduced by concurrent use of the SSRI citalopram
TL Lash, L Pedersen, D Cronin-Fenton, TP Ahern, CL Rosenberg, KL Lunetta, RA Silliman,
S Hamilton-Dutoit, JP Garne, M Ewertz, and HT Sørensen
Acta Oncologica, 2010; 49: 305–312
ORIGINAL ARTICLE
Breast cancer recurrence risk related to concurrent use of SSRI antidepressants and tamoxifen
DEIRDRE CRONIN-FENTON, THOMAS P. AHERN, REBECCA A. SILLIMAN, MARIANNE EWERTZ
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).
No Increase in Breast Cancer Recurrence with Concurrent Use of Tamoxifen and Some CYP2D6-Inhibiting Medications
Thomas P. Ahern,[1,2] Lars Pedersen,[2] Deirdre P. Cronin-Fenton,[2] Henrik Toft Sørensen,[1,2]
and Timothy L. Lash[1,2]
Eksempler på anden receptpligtig medicin?

AGENDA

- Introduktion
- Farmakoepidemiologi & databaser i Danmark
- Hvilken receptpligtig medicin snakker vi om?
- Et par eksempler af vores studier og resultater
- Styrker og begrænsninger
- Konklusioner & perspektiver

”Berit”

- 65 år gammel
- Brystkræftdiagnose i 2012
- Berit bruger aspirin for at forebygge hjertekarsygdomme, Simvastatin pga. forhøjet kolesterol og nogen gange Diklofenac mod artrit
- Berit er meget bekymret for om hun vil få tilbagefald af brystkræft... Og at hendes medicinbrug kan påvirke effekten af brystkræftbehandlingen.

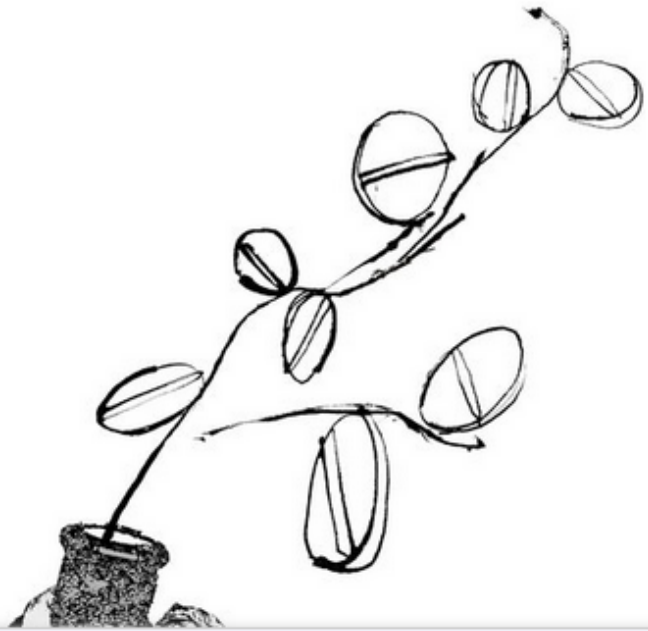
HOME SEARCH

The New York Times

The Opinion Pages | OP-ED CONTRIBUTORS

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.

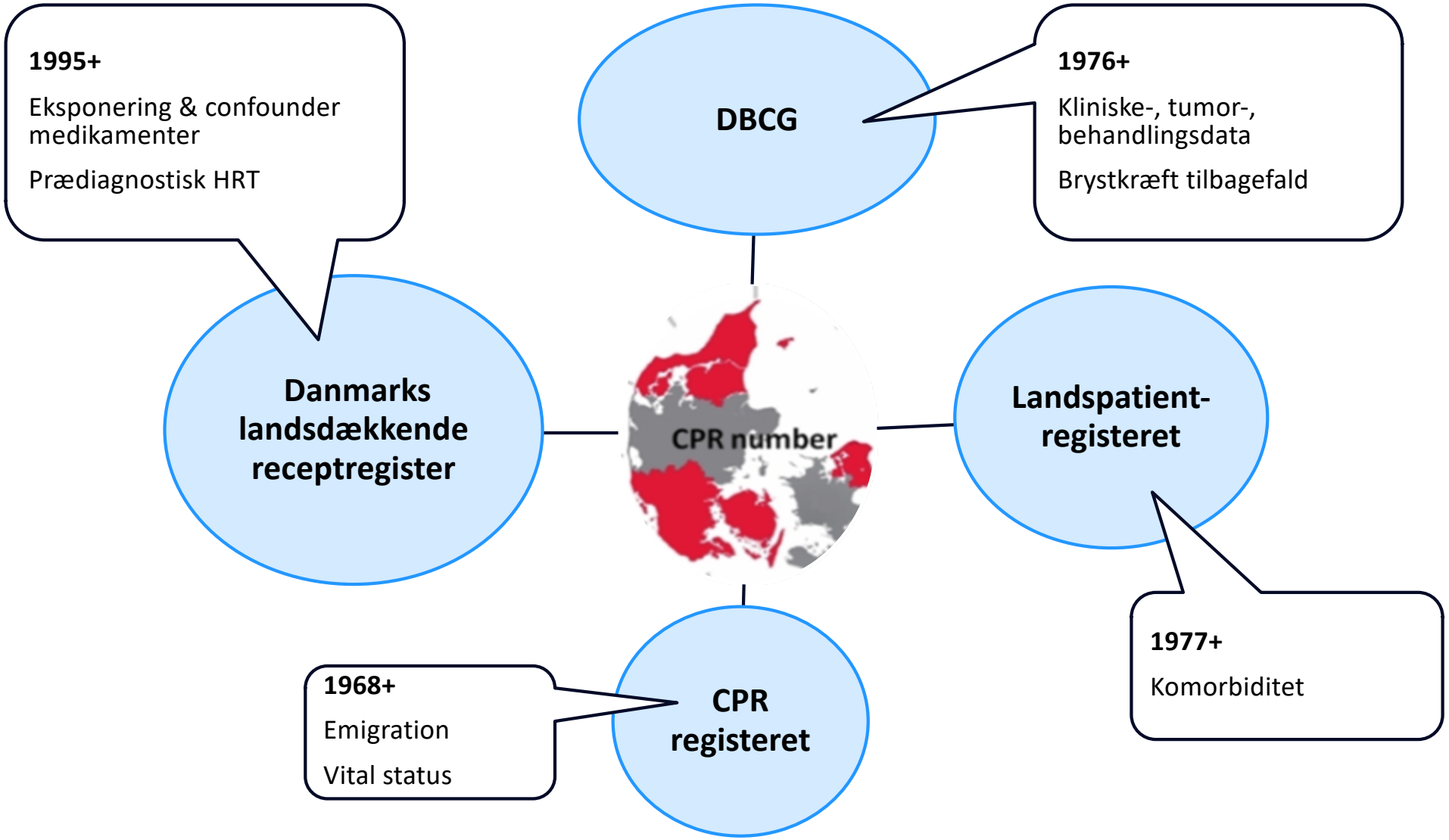
In 2010, we published an observational study in The Journal of Clinical Oncology showing that women with breast cancer who took aspirin at least once a week for various reasons were 50 percent less likely to die of breast cancer. In 2012, British

”FARMAKOEPIDEMIOLOGI”

At undersøge medicinbrug og effekten af medicinbrug i store populationer

Danske databaser til anvendelse indenfor, at man kan:

- undersøge bruge af lægemidler i store populationer tilbage i tiden og
- sammenkoble dette med andre befolkningsbaserede registre, fx. DBCG


1995+
Eksponering & confounder medikamenter
Prædiagnostisk HRT
DBCG
1976+
Kliniske-, tumor-, behandlingsdata
Brystkræft tilbagefald
Danmarks landsdækkende receptregister
CPR number
Landspatient-registeret
1977+
Komorbiditet
1968+
Emigration
Vital status
CPR registeret

TO EKSEMPLER:

(1) STATINER OG (2) ASPIRIN

OG RISIKOEN FOR

TILBAGEFALD AF BRYSTKRÆFT

BRUG AF STATINER OG RISIKOEN FOR TILBAGEFALD AF BRYSTKRÆFT

ARTICLE

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.

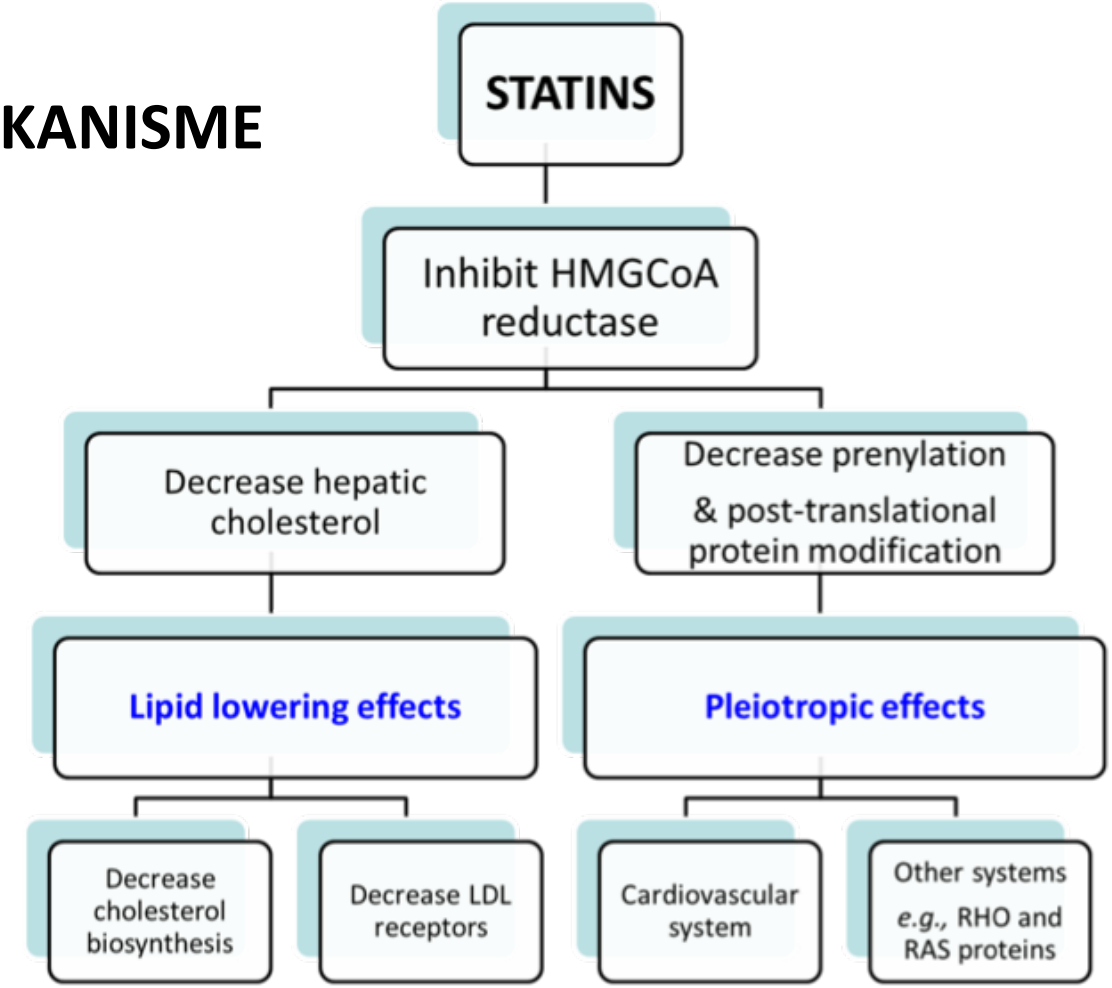
Methods We conducted a nationwide, population-based prospective cohort study of all female residents in Denmark diagnosed with stage I–III invasive breast carcinoma who were reported to the Danish Breast Cancer Cooperative Group registry between 1996 and 2003 (n = 18769). Women were followed for a median 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 menopausal status at diagnosis; histological grade; estrogen receptor status; receipt of adjuvant therapy; type of primary surgery received; pre-diagnosis hormone replacement therapy; and co-prescriptions of aspirin, angiotensin-converting enzyme inhibitors, nonsteroidal anti-inflammatory drugs, or anticoagulants. All statistical tests were two-sided.

Results Most prescriptions for lipophilic statins in the study population were for simvastatin. Exclusive simvastatin users experienced approximately 10 fewer breast cancer recurrences per 100 women after 10 years of follow-up (adjusted 10-year risk difference = −0.10, 95% confidence interval = −0.11 to −0.08), compared with women who were not prescribed a statin. Exclusive hydrophilic statin users had approximately the same risk of breast cancer recurrence as women not prescribed a statin over follow-up (adjusted 10-year risk difference = 0.05, 95% confidence interval = −0.01 to 0.11).

Conclusions Simvastatin, a highly lipophilic statin, was associated with a reduced risk of breast cancer recurrence among Danish women diagnosed with stage I–III breast carcinoma, whereas no association between hydrophilic statin use and breast cancer recurrence was observed.

J Natl Cancer Inst 2011;103:1461–1468

VIRKNINGSMEKANISME



LABORATORIE STUDIER AF STATINER

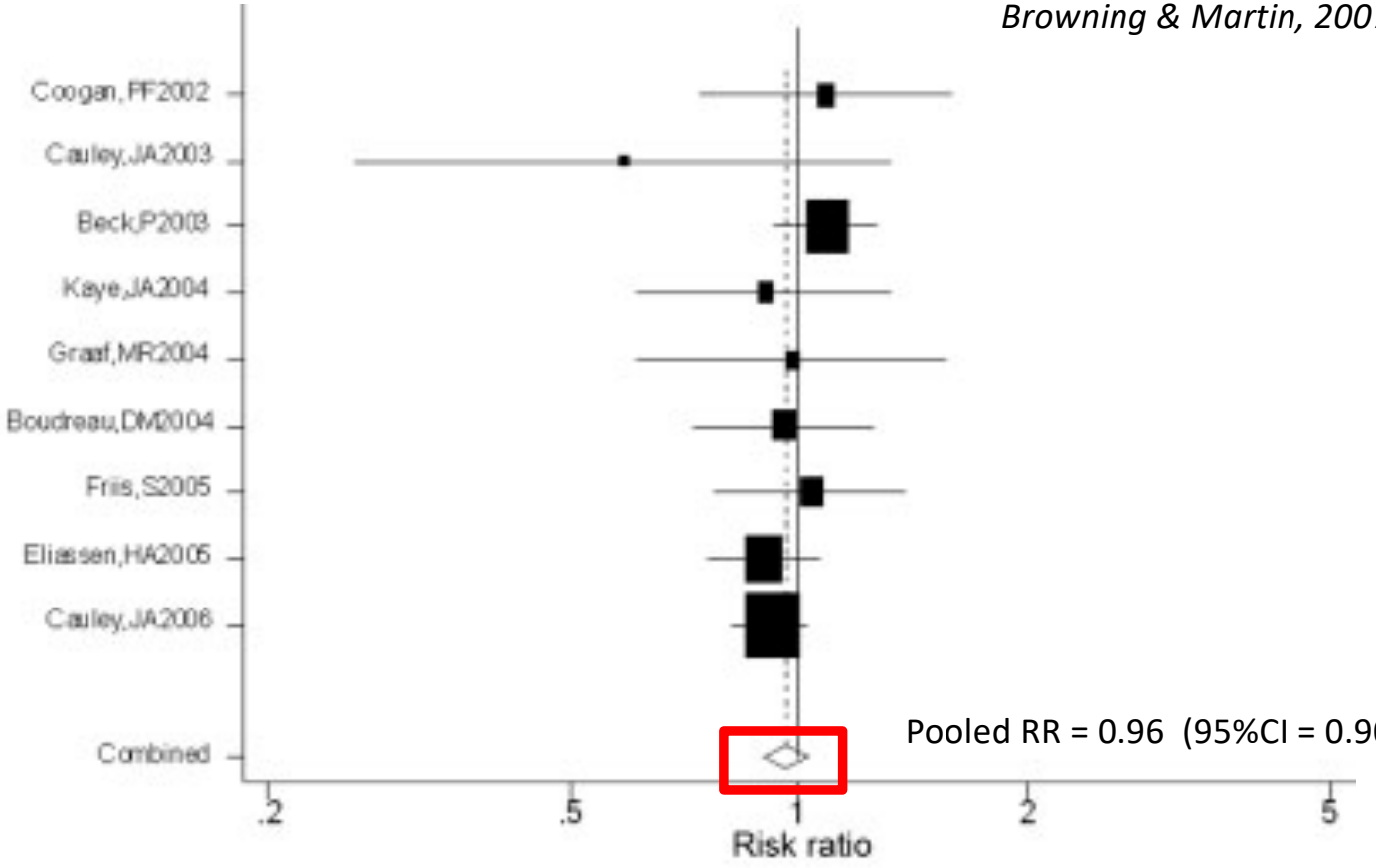
Forebygge mange cellulære processer – signaltransduktion, tumorvækst, angiogenese og metastaser

Inducere apoptosis

Lipofile statiner (Simvastatin, Fluvastatin) hæmmer væksten af brystkræftceller med 50%

STATINER & RISIKO FOR BRYSTKRÆFT

Browning & Martin, 2007



Pooled RR = 0.96 (95%CI = 0.90, 1.04)

STATINER & BRYSTKRÆFT TILBAGEFALD

To studier tyder på en bedre prognose blandt brystkræftpatienter, der bruger statiner *(Kwan et al., 2008 & Chae et al., 2011)*

Undersøgelser adskilte ikke typen af statiner (lipofil eller hydrofil)

Estimaterne var også upræcise pga. få patienter

Derudover var der immortal person-time bias i et studie*(Chae et al)*

Statin Prescriptions and Breast Cancer Recurrence Risk: A Danish Nationwide Prospective Cohort Study

J Natl Cancer Inst 2011;103:1461–1468

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

Mål:

At undersøge sammenhængen mellem statinbrug og risikoen for brystkræft tilbagefald

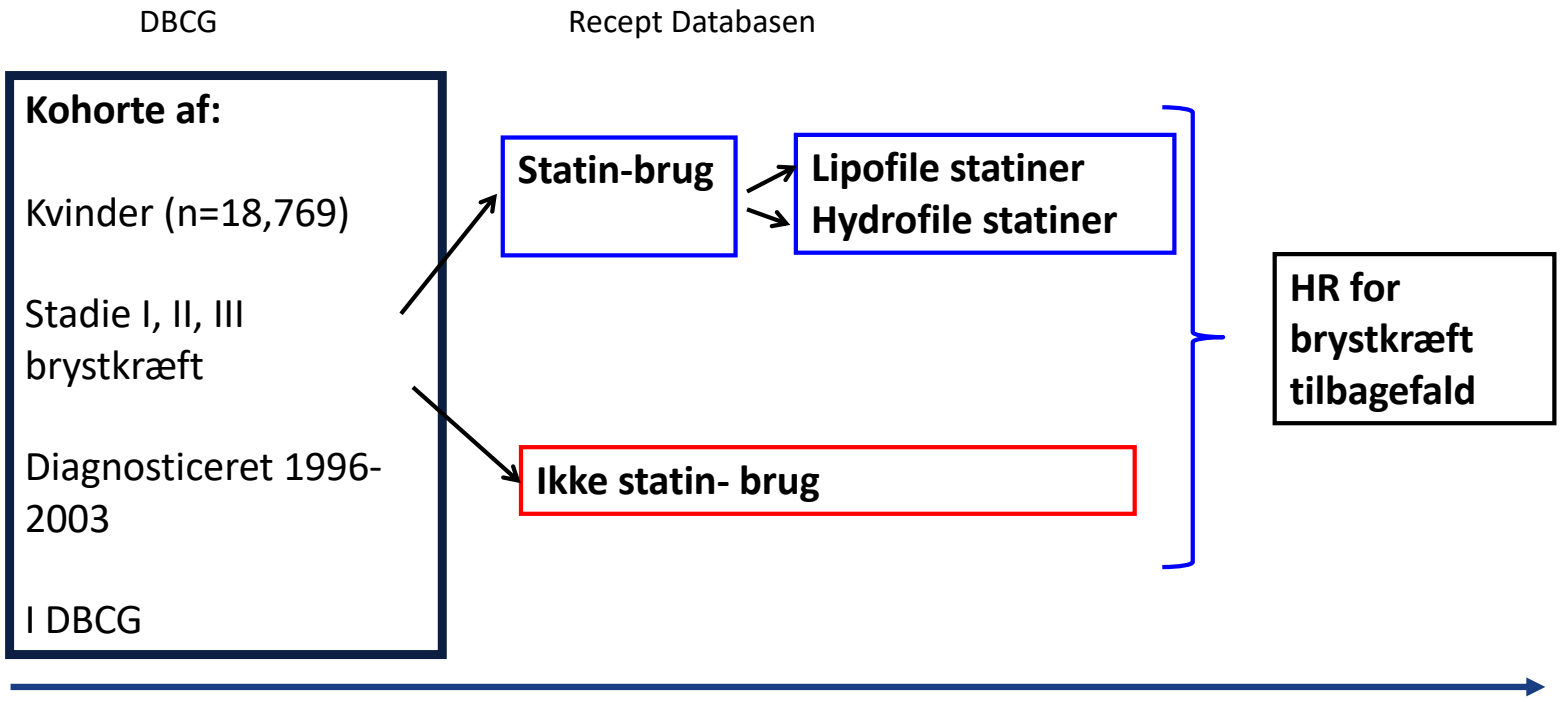
At undersøge denne sammenhæng med

Typen af statiner (lipofil versus hydrofil)

Hypotese:

Anvendelse af lipofile statiner, men ikke hydrofile statiner, nedsætter risikoen for tilbagefald af brystkræft

STUDIEPOPULATION & DATAKILDER



Opfølgning fra diagnosedato til recidiv, død, emigration, 10 år, eller 31/12/2008

STUDIEPOPULATIONEN

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)
Chemotherapy	657 (20)	4,816 (31)

STATINER & TILBAGEFALD AF BRYSTKRÆFT

Simvastatin:

Justeret HR= 0.70 (95% CI= 0.57, 0.86)

Hydrofile statiner:

Justeret HR = 1.2 (95% CI = 0.79, 1.7)

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Aspirin Intake and Survival After Breast Cancer

Michelle D. Holmes, Wendy Y. Chen, Lisa Li, Ellen Hertzmark, Donna Spiegelman, and Susan E. Hankinson

From the Channing Laboratory, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School; Department of Medical Oncology, Dana-Farber Cancer Institute; and Departments of Epidemiology and Biostatistics, Harvard School of Public Health, Boston, MA.

Submitted February 25, 2009; accepted December 9, 2009; published online ahead of print at www.jco.org on February 16, 2010.

Supported by National Institutes of Health Grant No. CA87969.

The National Institutes of Health had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; or preparation, review, and approval of the manuscript.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

Corresponding author: Michelle D. Holmes, MD, DrPH, Channing Laboratory, 181 Longwood Ave, Boston, MA 02115; e-mail: michelle.holmes@channing.harvard.edu.

A B S T R A C T

Purpose
Animal and in vitro studies suggest that aspirin may inhibit breast cancer metastasis. We studied whether aspirin use among women with breast cancer decreased their risk of death from breast cancer.

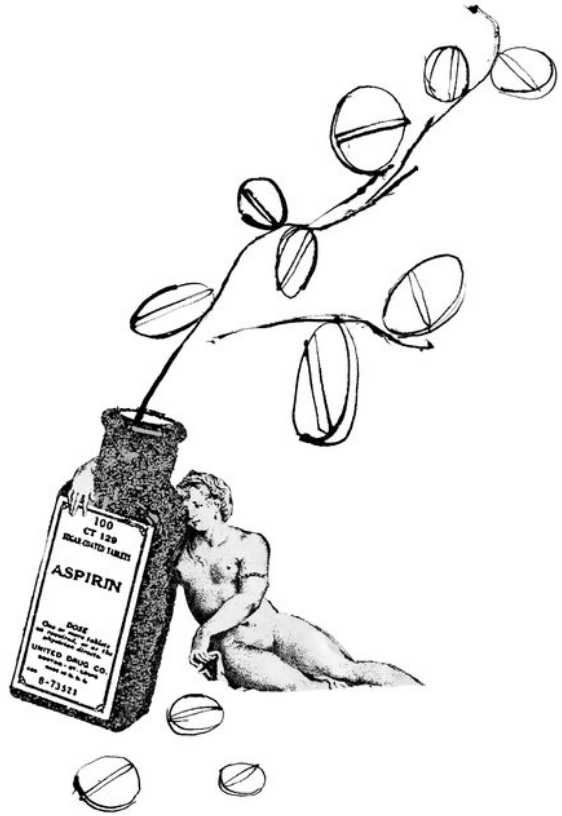
Methods
This was a prospective observational study based on responses from 4,164 female registered nurses in the Nurses' Health Study who were diagnosed with stages I, II, or III breast cancer between 1976 and 2002 and were observed until death or June 2006, whichever came first. The main outcome was breast cancer mortality risk according to number of days per week of aspirin use (0, 1, 2 to 5, or 6 to 7 days) first assessed at least 12 months after diagnosis and updated.

Results
There were 341 breast cancer deaths. Aspirin use was associated with a decreased risk of breast cancer death. The adjusted relative risks (RRs) for 1, 2 to 5, and 6 to 7 days of aspirin use per week compared with no use were 1.07 (95% CI, 0.70 to 1.63), 0.29 (95% CI, 0.16 to 0.52), and 0.36 (95% CI, 0.24 to 0.54), respectively (test for linear trend, $P < .001$). This association did not differ appreciably by stage, menopausal status, body mass index, or estrogen receptor status. Results were similar for distant recurrence. The adjusted RRs were 0.91 (95% CI, 0.62 to 1.33), 0.40 (95% CI, 0.24 to 0.65), and 0.57 (95% CI, 0.39 to 0.82; test for trend, $P = .03$) for 1, 2 to 5, and 6 to 7 days of aspirin use, respectively.

Conclusion
Among women living at least 1 year after a breast cancer diagnosis, aspirin use was associated with a decreased risk of distant recurrence and breast cancer death.

J Clin Oncol 28:1467-1472.

BRUG AF ASPIRIN OG RISIKO FOR BRYSTKRÆFTTILBAGEFALD



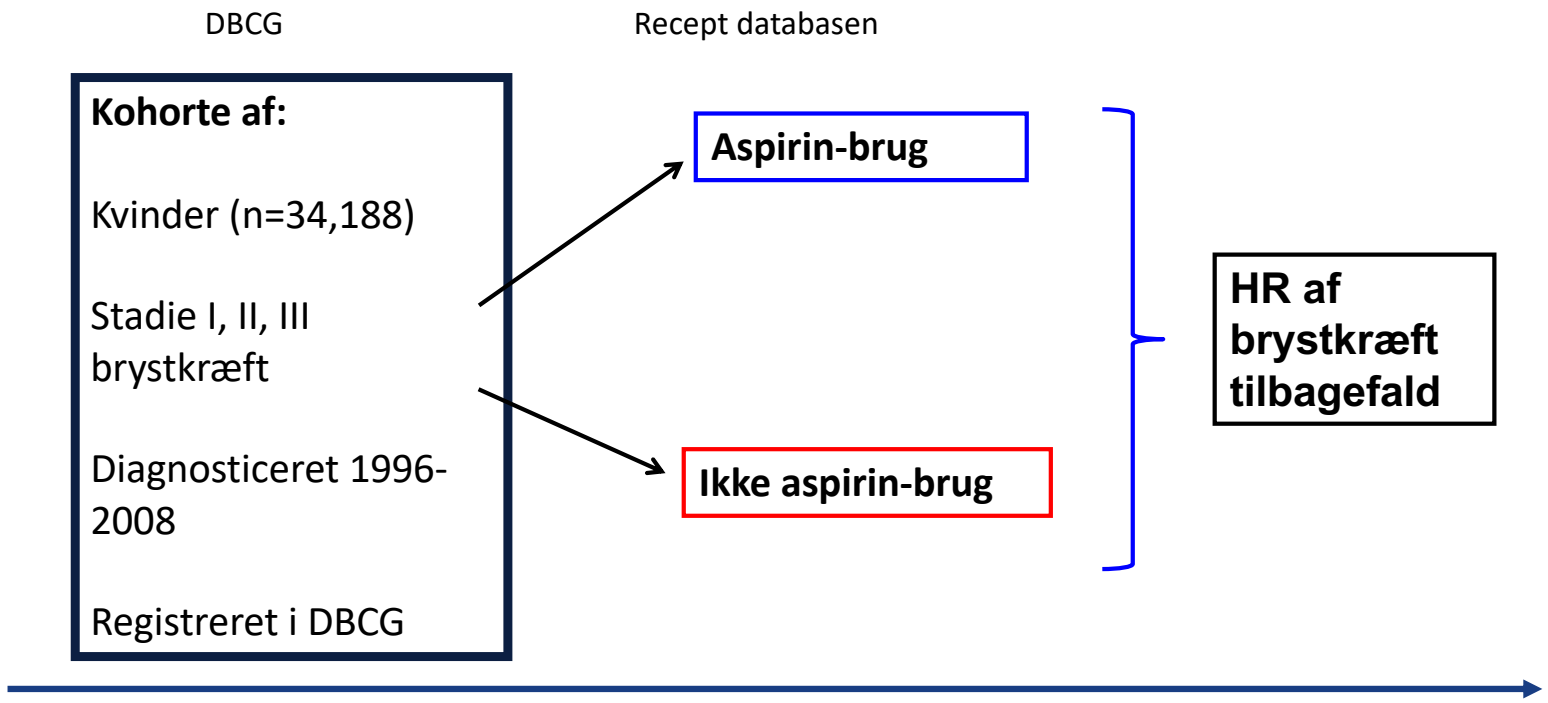
Formål:

- At undersøge sammenhængen mellem aspirinbrug (NSAIDs, og sCOX-2i) og brystkræftilbagefald

Hypotese:

- Aspirinbrug er associeret med en nedsat risiko for tilbagefald sammenlignet med ikke-brug.

STUDIEPOPULATION & DATAKILDER



RECEPTPLIGTIG MEDICIN: DEFINITION AF EKSPONERING

Lav-dosis aspirin: >=1 recept hvert år, opdateret dagligt & forskudt 1 år

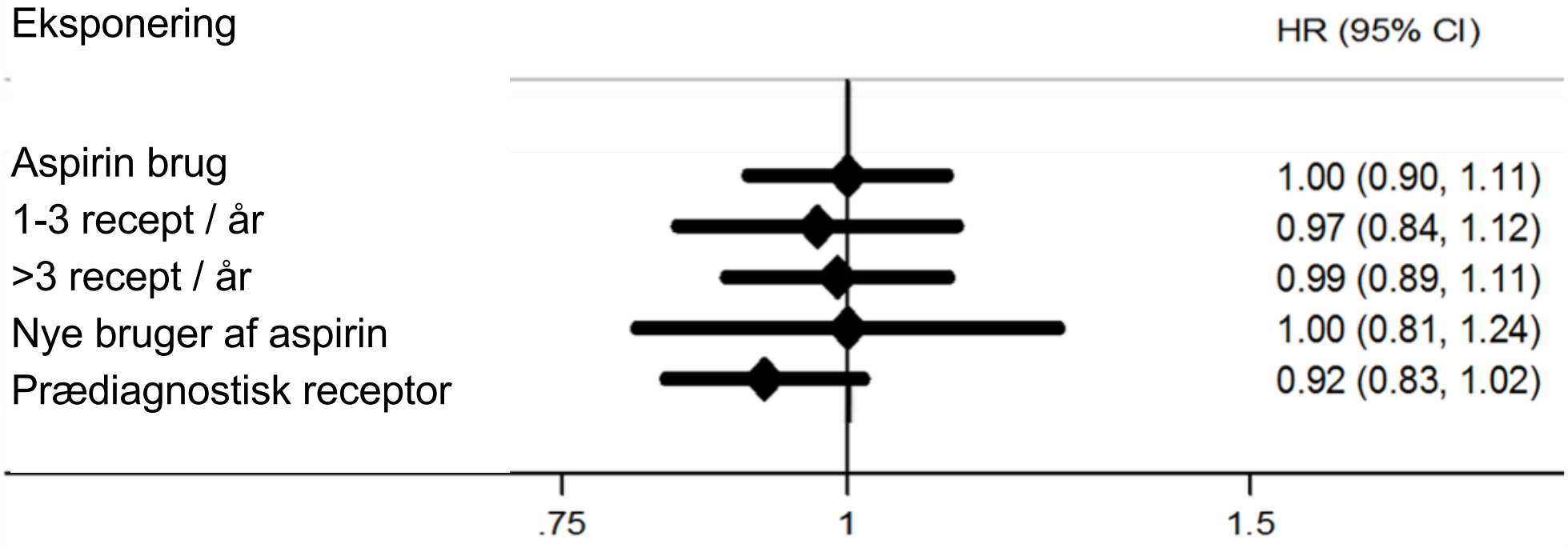
”Nye brugere”: >=5 års recepthistorie, ingen brug prædiagnostisk

Dosis-respons: Antal recepter

Præ-diagnostisk brug: Kvinder med >=2 års recept historie

Co medikamenter: Post-diagnostisk tidsafhængig Simvastatinbrug og præ-diagnostisk HRT-brug

Eksponering



Low-dose Aspirin, Nonsteroidal Anti-inflammatory Drugs, Selective COX-2 Inhibitors and Breast Cancer Recurrence

Deirdre P. Cronin-Fenton,[a] *Uffe Heide-Jørgensen,*[a] *Thomas P. Ahern,*[b] *Timothy L. Lash,*[a,c] *Peer Christiansen,*[d,e] *Bent Ejlertsen,*[e,f] *and Henrik T. Sørensen*[a]

Background: Aspirin, nonsteroidal anti-inflammatory drugs (NSAIDs), and selective COX-2 inhibitors may improve outcomes in breast cancer patients. We investigated the association of aspirin, NSAIDs, and use of selective COX-2 inhibitors with breast cancer recurrence.

Methods: We identified incident stage I–III Danish breast cancer patients in the Danish Breast Cancer Cooperative Group registry, who were diagnosed during 1996–2008. Prescriptions for aspirin (>99% low-dose aspirin), NSAIDs, and selective COX-2 inhibitors were ascertained from the National Prescription Registry. Follow-up began on the date of breast cancer primary surgery and continued until the first of recurrence, death, emigration, or 1 January 2013. We used Cox regression models to compute hazard ratios (HR) and corresponding 95% confidence intervals (95% CI) associating prescriptions with recurrence, adjusting for confounders.

Results: We identified 34,188 breast cancer patients with 233,130 person-years of follow-up. Median follow-up was 7.1 years; 5,325 patients developed recurrent disease. Use of aspirin, NSAIDs, or selective COX-2 inhibitors was not associated with the rate of recurrence ($HR_{adjusted}$ aspirin = 1.0, 95% CI = 0.90, 1.1; NSAIDs = 0.99, 95% CI = 0.92, 1.1; selective COX-2 inhibitors = 1.1, 95% CI = 0.98, 1.2), relative to nonuse. Prediagnostic use of the exposure drugs was associated with reduced recurrence rates ($HR_{aspirin}$ = 0.92, 95% CI = 0.82, 1.0; HR_{NSAIDs} = 0.86, 95% CI = 0.81, 0.91; $HR_{sCOX\text{-}2inhibitors}$ = 0.88, 95% CI = 0.83, 0.95).

Conclusions: This prospective cohort study suggests that post diagnostic prescriptions for aspirin, NSAIDs, and selective COX-2 inhibitors have little or no association with the rate of breast cancer recurrence. Prediagnostic use of the drugs was, however, associated with a reduced rate of breast cancer recurrence.

(*Epidemiology* 2016;27: 586–593)

Submitted 22 June 2015; accepted 21 March 2016.

From the [a]Department of Clinical Epidemiology, Aarhus University, Aarhus, Denmark; [b]Departments of Surgery and Biochemistry, University of Vermont, Burlington, VT; [c]Department of Epidemiology, Rollins School of Public Health, Emory University, Atlanta, GA; [d]Breast and Endocrine Section, Department of Surgery, Aarhus University Hospital, Aarhus, Denmark; [e]Danish Breast Cancer Cooperative Group, Copenhagen, Denmark; and [f]Rigshospitalet, Copenhagen, Denmark.

The study was supported by grants from the Danish Cancer Society (R73-A4284-13-S17) (H.T.S.); the Aarhus University Research Foundation

HVORFOR ER DET EN FORDEL AT BRUGE DANSK DATA OG DBCG DATA?

STYRKER

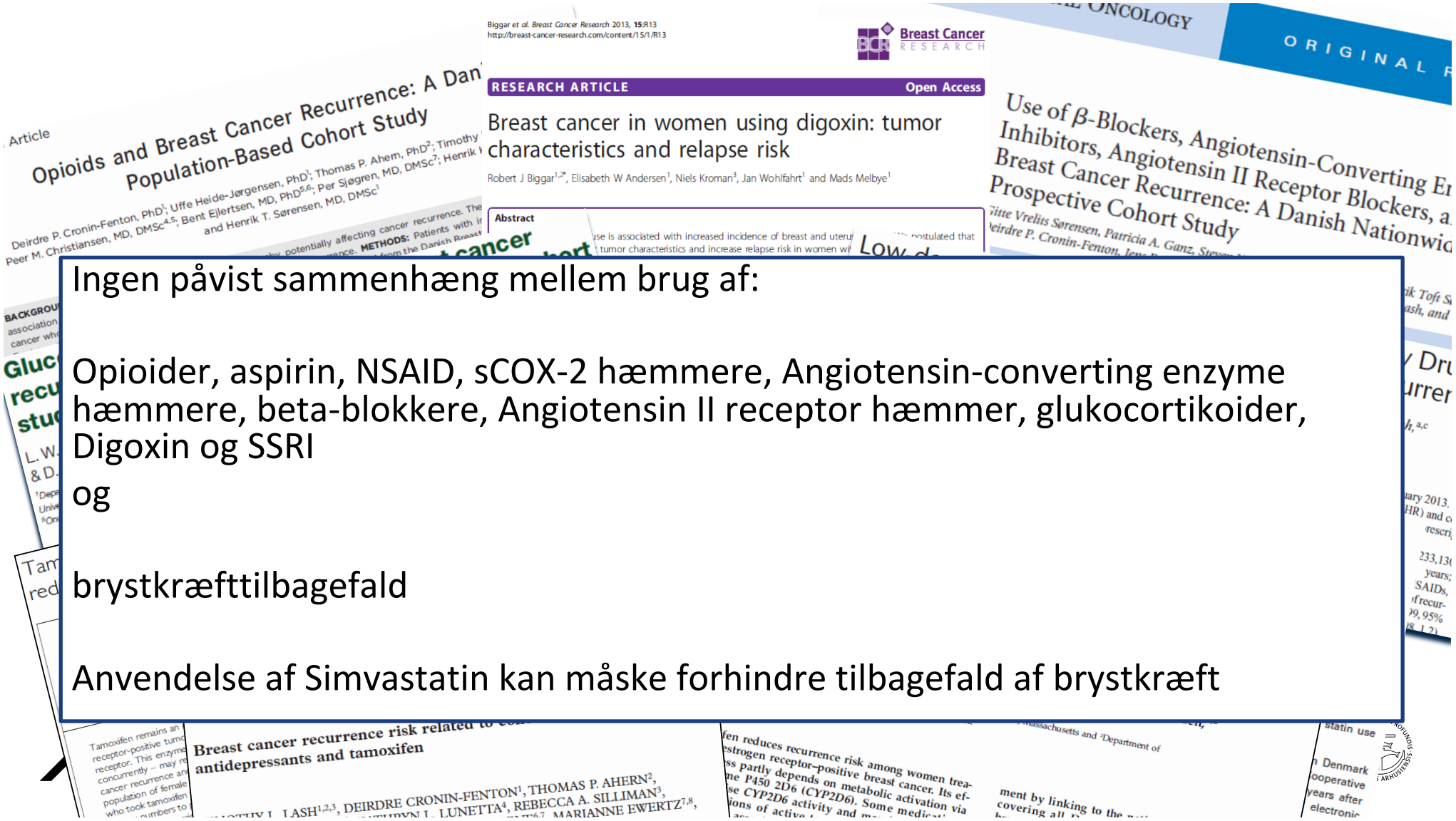
- Sammenkobling på individniveau på tværs af andre danske databaser
- Justering for potentielle confoundere, herunder co-medikamenter samt komorbiditet
- Mulighed for store og landsdækkende kohorter
- Høj datakvalitet & komplethed
- Ingen selektionsbias
- Ingen selvrapporteret medicin data og dermed ingen recall bias
- Rutineregistrering af brystkræfttilbagefald
  - Tilbagefald af brystkræft er et cancerspecifikt endepunkt: vi kan derfor undersøge den specifikke effekt af lægemidlerne på kræft i stedet for på dødelighed generelt

BEGRÆNSNINGER

- Medicin compliance
- Ingen information om medicinbrug under indlæggelse
- Ingen information om håndkøbsmedicin

KONKLUSION OG PERSPEKTIVER

Konklusioner på anden receptpligtig medicin?



Ingen påvist sammenhæng mellem brug af:

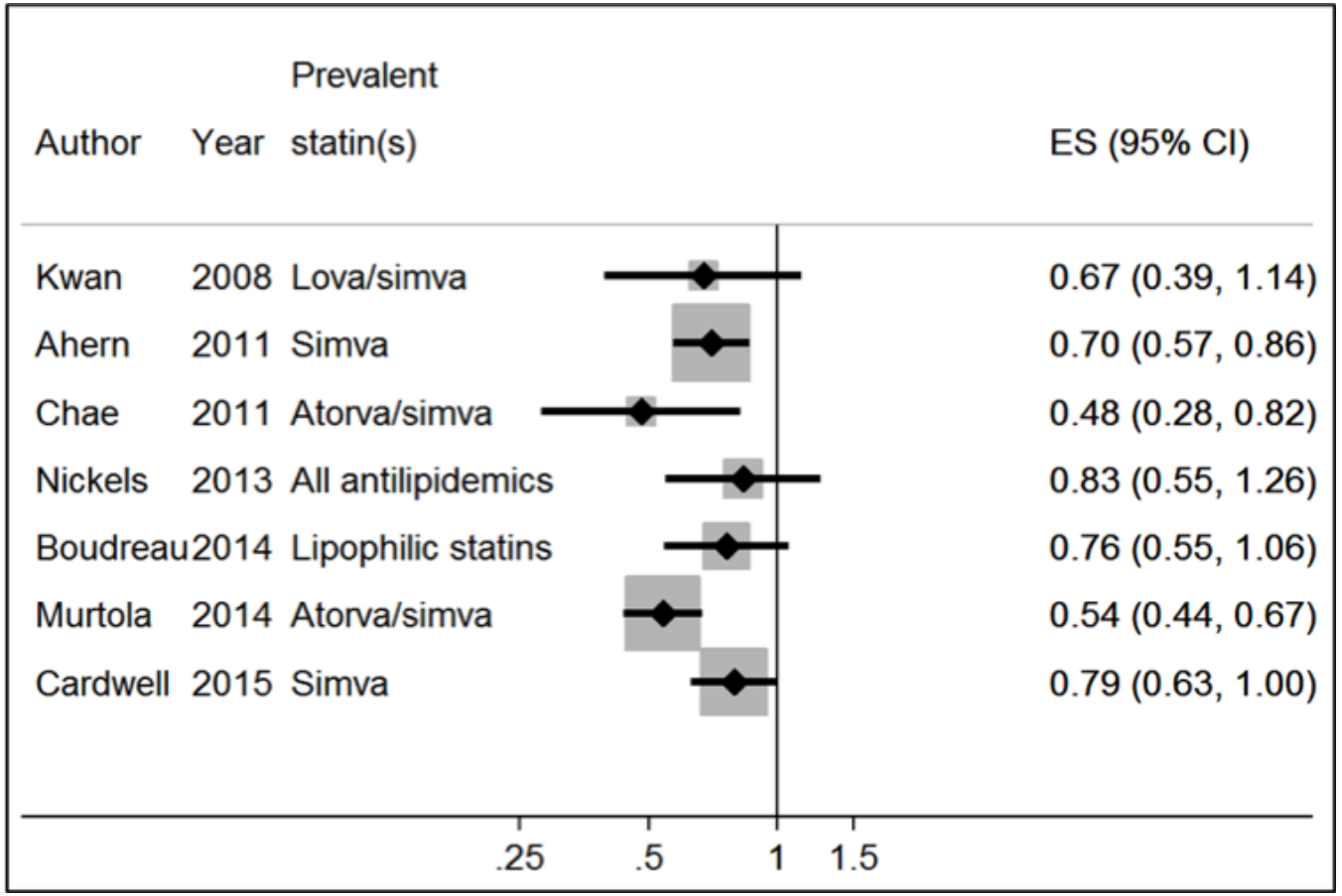
Opioider, aspirin, NSAID, sCOX-2 hæmmere, Angiotensin-converting enzyme hæmmere, beta-blokkere, Angiotensin II receptor hæmmer, glukocortikoider, Digoxin og SSRI

og

brystkræfttilbagefald

Anvendelse af Simvastatin kan måske forhindre tilbagefald af brystkræft

OBSERVATIONELLE STUDIER



Adapted from Ahern et al., Lancet Oncology 2014

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JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

POST-HOC ANALYSER I RCT (BIG-1-98)

Cholesterol, Cholesterol-Lowering Medication Use, and Breast Cancer Outcome in the BIG 1-98 Study

Signe Borgquist, Anita Giobbie-Hurder, Thomas P. Ahern, Judy E. Garber, Marco Colleoni, István Láng, Marc Debled, Bent Ejlertsen, Roger von Moos, Ian Smith, Alan S. Coates, Aron Goldhirsch, Manuela Rabaglio, Karen N. Price, Richard D. Gelber, Meredith M. Regan, and Beat Thürlimann

Author affiliations and support information (if applicable) appear at the end of this article.

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Clinical trial information: NCT00004205.

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0732-183X/17/3511w-1179w/$20.00

A B S T R A C T

Purpose

Cholesterol-lowering medication (CLM) has been reported to have a role in preventing breast cancer recurrence. CLM may attenuate signaling through the estrogen receptor by reducing levels of the estrogenic cholesterol metabolite 27-hydroxycholesterol. The impact of endocrine treatment on cholesterol levels and hypercholesterolemia per se may counteract the intended effect of aromatase inhibitors.

Patients and Methods

The Breast International Group (BIG) conducted a randomized, phase III, double-blind trial, BIG 1-98, which enrolled 8,010 postmenopausal women with early-stage, hormone receptor–positive invasive breast cancer from 1998 to 2003. Systemic levels of total cholesterol and use of CLM were measured at study entry and every 6 months up to 5.5 years. Cumulative incidence functions were used to describe the initiation of CLM in the presence of competing risks. Marginal structural Cox proportional hazards modeling investigated the relationships between initiation of CLM during endocrine therapy and outcome. Three time-to-event end points were considered: disease-free-survival, breast cancer–free interval, and distant recurrence–free interval.


POLITIKEN
SEKTIONER
SØG
DIT POLITIKEN
MERE
FORBRUG & LIV
Bolig Sundhed Digitalt Forbrug Biler Livsstil Guider Test
SUNDHED 25. JAN. 2012 KL. 09.00
Kolesterolpiller kan hjælpe mod brystkræft
Dansk undersøgelse viser, at kolesterolmedicin måske forhindrer tilbagefald hos kvinder med brystkræft.
BERLINGSKE
Få Berlingske hver dag i 3 mdr. for 249 kr.
Foto: Kristian Brasen
Kolesterolpiller øger kræftoverlevelse
Af Marianne Fajstrup
7. november 2012, 22:30
Kræftpatienter, der tager kolesterolsænkende medicin, har bedre chance for at overleve. Ny dansk forskning viser sammenhæng mellem statiner og kræft, som skal undersøges nærmere.
DAGENS Medicin
Nyheder Videnskab Almen praksis Karriere Blogs
Kræft Hjerte-kar Psykiatri Diabetes Kvindesygdomme
Opdateret 19.11.2012 Videnskab: Cancer
Statiner øger overlevelseschancer hos kræftpatienter
Nyt dansk studie viser, at patient
kræft.

TAK TIL

DBCG
Kræftens Bekæmpelse (R73-A4284-13-S17)
Aarhus Universitets Forskningsfond
Lundbeck Fonden (R167-2013-15861)
Elvira & Rasmus Riisforts Fond
Susan G. Komen for Cure (CCR 13264024)
US NIH (R01CA166825)

SAMARBEJDSPARTNERE

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DBCG: Peer Christiansen, Bent Ejlertsen

Odense University: Per Damkier, Marianne Ewertz

Emory University: Tim Lash, Mike Zwick

Boston University: Rebecca Silliman

University of Vermont: Thomas Ahern

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