Department of Clinical Epidemiology

Markører for nedsat immunforsvar og risiko for tilbagefald af brystkræft

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DBCG årsmøde

18. Januar 2016

Studie A Glukokortikoid og recidiv

Studie B Autoimmun og recidiv

Studie C Alder og lymfeknudestatus

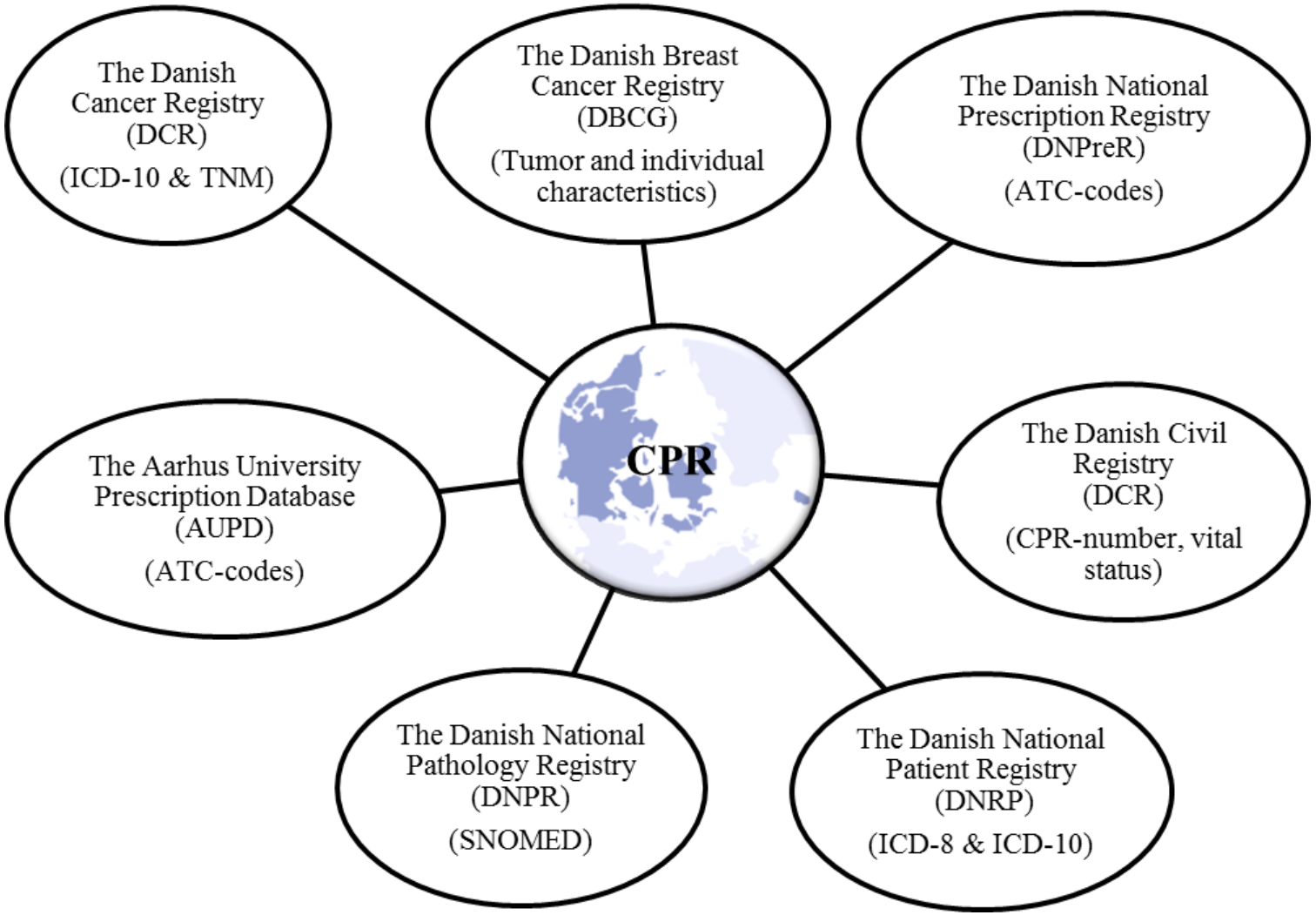
Markører for immunfunktion

Zhang C *et al* **Int J Oncol** (2006)
Ferrand N *et al* **Biochem J** (2012)

Hemminki K *et al* **Gynecol Oncol (**2012)

Wildiers H *et al* **J Clin Oncol (**2009)

Administrative og kliniske registre



Studie A: Glukokortikoid og recidiv

original article

Annals of Oncology 00: 1–6, 2014
doi:10.1093/annonc/mdu453

Glucocorticoid prescriptions and breast cancer recurrence: a Danish nationwide prospective cohort study

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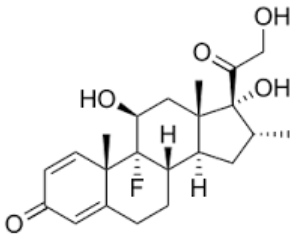
Background: Treatment with synthetic glucocorticoids (GCs) depresses the immune response and may therefore modify cancer outcomes. We investigated the association between GC use and breast cancer recurrence.

Materials and methods: We conducted a population-based cohort study to examine the risk of breast cancer recurrence associated with GC use among incident stage I–III female breast cancer patients aged >18 years diagnosed 1996–2003 in Denmark. Data on patients, clinical and treatment factors, recurrence, and comorbidities as well as data on GC prescriptions and potential confounders were obtained from Danish population-based medical registries. GCs were categorized according to administrative route: systemic, inhaled, or intestinal. Women were followed for up to 10 years or until 31 December 2008. We used Cox proportional hazards regression models to compute hazard ratios (HRs) and associated 95% confidence intervals (95% CIs) to evaluate the association between GC use and recurrence. Time-varying drug exposures were lagged by 1 year.

Glukokortikoider

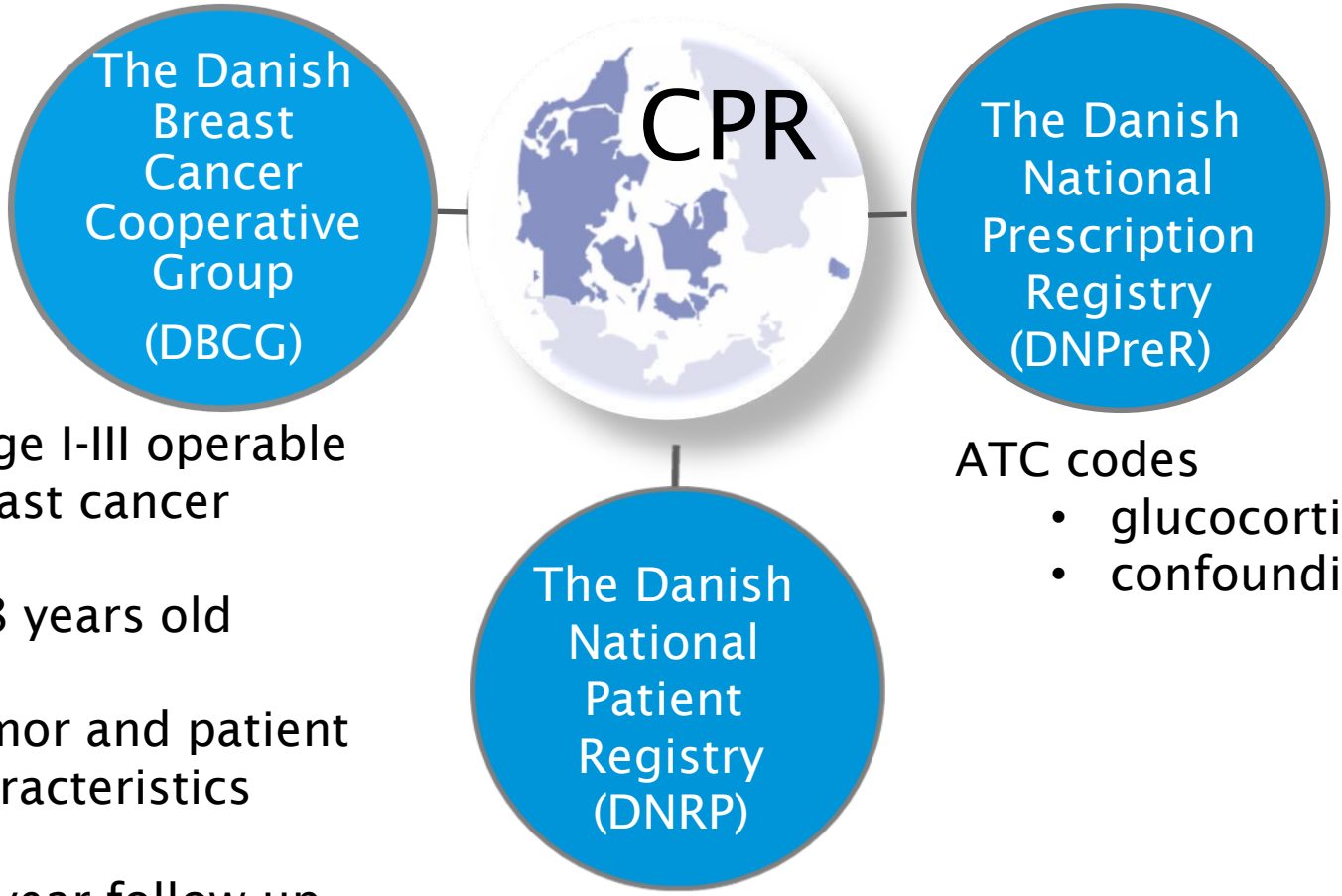


Anti-inflammatorisk
Immunsupprimerende

- Systemisk: piller og injektioner
- Inhalationspræperater
- Skum og suppositorier til brug i tarmen

Rutz HP *et al* **Cancer Biol Ther** (2004)
Rutz HP *et al* **Cancer** (2005)
Zhang C *et al* **Int J Oncol** (2006)
Ferrand N *et al* **Biochem J** (2012)

1996-2003



Stage I-III operable breast cancer

≥18 years old

Tumor and patient characteristics

10 year follow-up incl. recurrence

ATC codes
- glucocorticoids
- confounding drugs

ICD-codes
potential confounding diseases

N=18,251

Resultater

	Unadjusted[§] HR (95% CI)		Adjusted[§*] HR (95% CI)	
Systemic GC	1.1 (0.9,1.3)		1.1 (0.9,1.3)	
Inhaled GC	0.9 (0.7,1.0)		0.9 (0.7,1.0)	
Intestinal GC	1.0 (0.9,1.2)		1.0 (0.8,1.2)	
	Chemotherapy	**No chemotherapy**	**Chemotherapy**	**No chemotherapy**
Systemic GC	1.1 (0.9, 1.4)	1.0 (0.9, 1.2)	1.1 (0.9, 1.4)	1.0 (0.8, 1.2)
Inhaled GC	0.9 (0.6, 1.2)	0.9 (0.7, 1.1)	0.9 (0.6, 1.3)	0.8 (0.7, 1.0)
Intestinal GC	0.9 (0.7, 1.2)	1.1 (0.9, 1.3)	0.9 (0.6, 1.2)	1.0 (0.8, 1.3)
	ER positive	**ER negative**	**ER positive**	**ER negative**
Systemic GC	1.1 (0.9,1.3)	1.1(0.8,1.4)	1.1(0.9,1.3)	1.0(0.8,1.4)
Inhaled GC	0.9 (0.7,1.1)	0.8(0.6,1.2)	0.8(0.7,1.0)	1.0(0.7,1.4)
Intestinal GC	1.0 (0.8,1.2)	1.0(0.7,1.4)	1.0(0.8,1.2)	1.0(0.7,1.4)
Prednisolone-equivalent dose**				
1-999 mg	0.9 (0.8, 1.0)		0.9 (0.8, 1.1)	
1000-4999 mg	0.9 (0.8, 1.1)		0.8 (0.7, 1.0)	
≥5000 mg	1.0 (0.7, 1.5)		0.9 (0.6, 1.4)	
Cumulative increase in duration of GC exposure over a 10-year period ^	1.0 (0.9, 1.0)		1.1 (0.9, 1.3)	

Studie B: Autoimmune sygdomme og recidiv

Breast Cancer Res Treat
DOI 10.1007/s10549-014-3258-2

EPIDEMIOLOGY

Autoimmune diseases and breast cancer recurrence: a Danish nationwide cohort study

Lone Winther Lietzen · Deirdre Cronin-Fenton · Peer Christiansen · Henrik Toft Sørensen · Timothy L. Lash

Received: 19 December 2014 / Accepted: 21 December 2014

Abstract Autoimmune diseases (ADs) comprise a large group of heterogeneous diseases in which the immune system attacks healthy organs. Both intrinsic changes in the body and AD treatment can compromise immune function. Impaired immune function could increase the risk of recurrent cancer. We aimed to investigate this hypothesis in a population-based epidemiological study. We examined the risk of breast cancer (BC) recurrence associated with an AD diagnosis among patients with incident stages I–III BC diagnosed during 1980–2007. Data were obtained from Danish population-based medical registries. ADs were categorized dichotomously and according to organ system of origin. Follow-up was up to 10 years or until 31 December 2009. Multivariate Cox proportional hazard recurrence during follow-up. 6,716 women had at least one AD. In adjusted models, the association between ADs and BC recurrence was near null: $HR_{adjusted}$ 0.96 (95 % CI 0.89, 1.04). These results held in all AD subcategories, except for central nervous/neuromuscular system ADs, with $HR_{adjusted}$ 0.56 (95 % CI 0.40, 0.78). Among women with BC, a history of at least one AD diagnosis was not associated with BC recurrence, with the possible exception of ADs of the central nervous/neuromuscular system.

Keywords Autoimmune diseases · Breast neoplasm · Clinical epidemiology · Outcome/recurrence · Denmark

1980-2007

Stage I-III operable breast cancer

≥18 years old

Tumor and patient characteristics

10 year follow-up and incl. recurrence

ICD-codes of

- 30 Autoimmune diseases
- modified Charlson Comorbidity Index

N=78,095

Kohorten

78,095 kvinder

Median alder 61 (19-102)

13,545 (17%) fik recidiv

6,716 (9%) med autoimmune sygdom

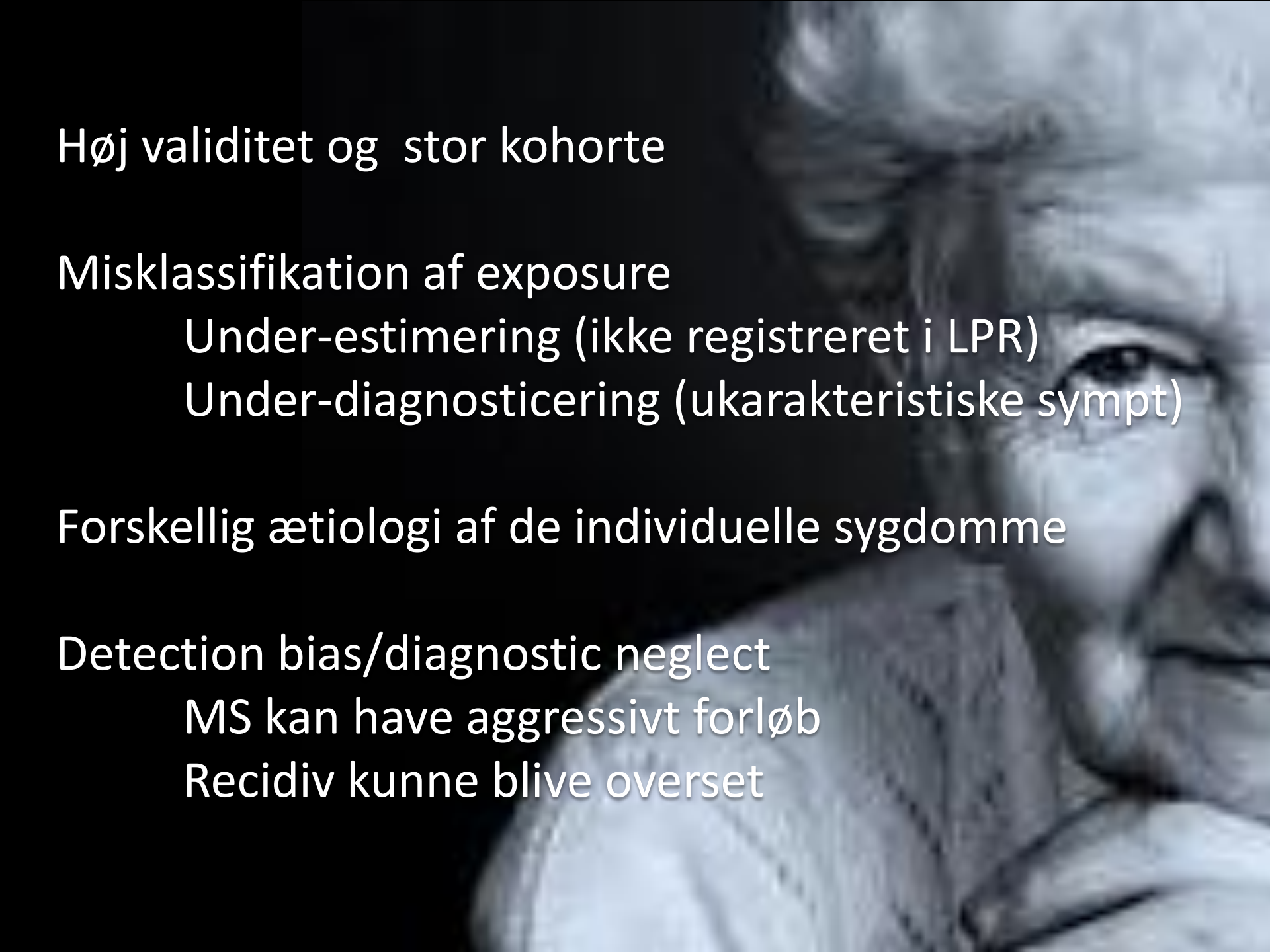
Crude Hazard Ratio
0.83 (0.77, 0.89)

Adjusted Hazard Ratio
0.96 (0.89, 1.04)

alder, stadie, kemo, kirurgi, menopausestatus, CCI
competing-risk-of-death model

Kategorier

	N	$HR_{adjusted}$ (95% CI)
Benigne blodsygdomme	69	0.96 (0.89, 1.04)
Mave-tarmsygdomme	872	0.87 (0.70, 1.07)
Hudsygdomme	399	0.92 (0.71, 1.24)
Bindevævssygdomme	2,369	1.11 (0.98, 1.25)
Endokrine sygdomme	2,704	0.98 (0.87, 1.10)
CNS/neuromuskulære sygd.	297	0.56 (0.40, 0.78)



Høj validitet og stor kohorte

Misklassifikation af exposure

- Under-estimering (ikke registreret i LPR)
- Under-diagnosticering (ukarakteristiske sympt)

Forskellig ætiologi af de individuelle sygdomme

Detection bias/diagnostic neglect

- MS kan have aggressivt forløb
- Recidiv kunne blive overset

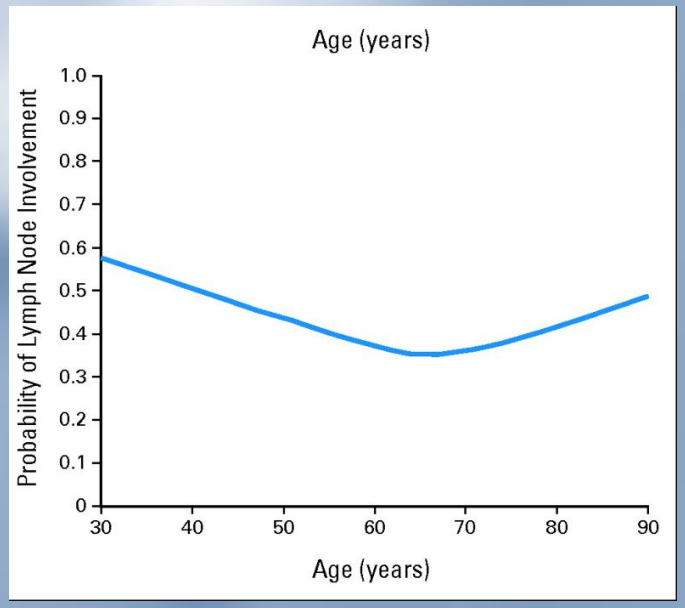
Studie C: Alder og lymfeknudestatus

Age at Diagnosis and Proportion of Node–Positive Breast Cancer Cases: A Danish Population–based Study

Authors Lone Winther Lietzen,[1] Deirdre P. Cronin–Fenton,[1] Peer Christiansen,[2] Henrik Toft Sørensen,[1] Bent Ejlertsen,[3] Rebecca A. Silliman,[4] Timothy L. Lash[1,5]

[1]Department of Clinical Epidemiology, Aarhus University, Aarhus, Denmark [2] Department of Surgery P, Aarhus University Hospital, Aarhus, Denmark [3] DBCG Secretariat, Copenhagen University Hospital, Aarhus, Denmark [4] Department of Medicine, Boston University School of Medicine, Boston, USA [5] Department of Epidemiology, Rollins School of Public Health, Emory University, Atlanta, USA

Abstract word count: 258
Text word count: 2,626
Number of tables: 1
Number of figures: 3
Number of appendix: 1
Running title: Age and lymph node–positive breast cancer



Alder ≤70 havde faldende risiko for positive lymfeknude med stigende alder

Alder >70 havde stigende risiko for positiv lymfeknude med stigende alder

Immunosenescense?

Wildiers H *et al*. **J Clin Oncol** (2009)
Voogd AC *et al*. **J Clin Oncol** (2009)
Mamounas EP *et al*. **J Clin Oncol** (2009)

2000-2013

Invasive breast cancer

≥18 years old

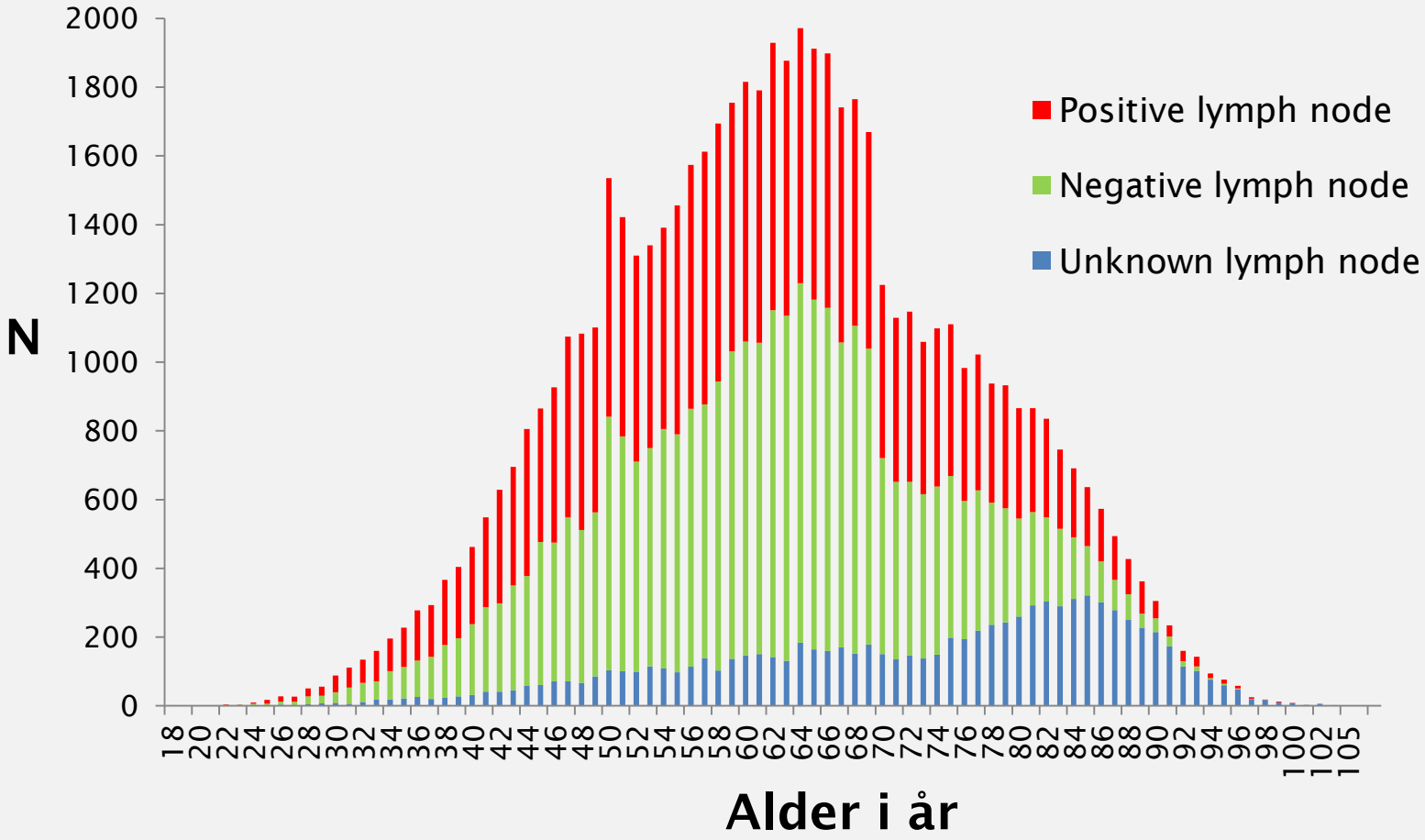
Lymph node status

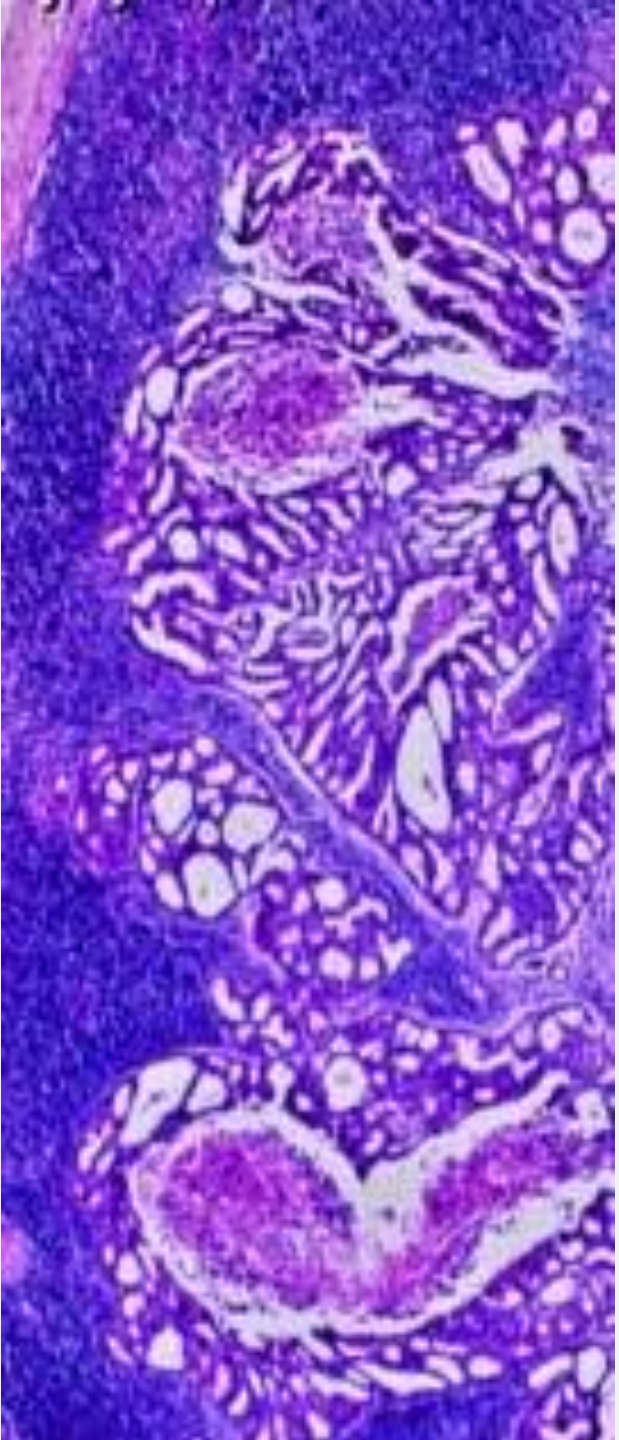
SNOMED codes of invasive breast cancer

Lymph node status

N=62,393

Alder og lymfeknudestatus





Konklusion

Ingen konklusion om Immunosenescenceteorien

Det belgiske studie kan heller ikke konkludere noget

Wildiers H *et al*. **J Clin Oncol** (2009)
Voogd AC *et al*. **J Clin Oncol** (2009)
Mamounas EP *et al*. **J Clin Oncol** (2009)

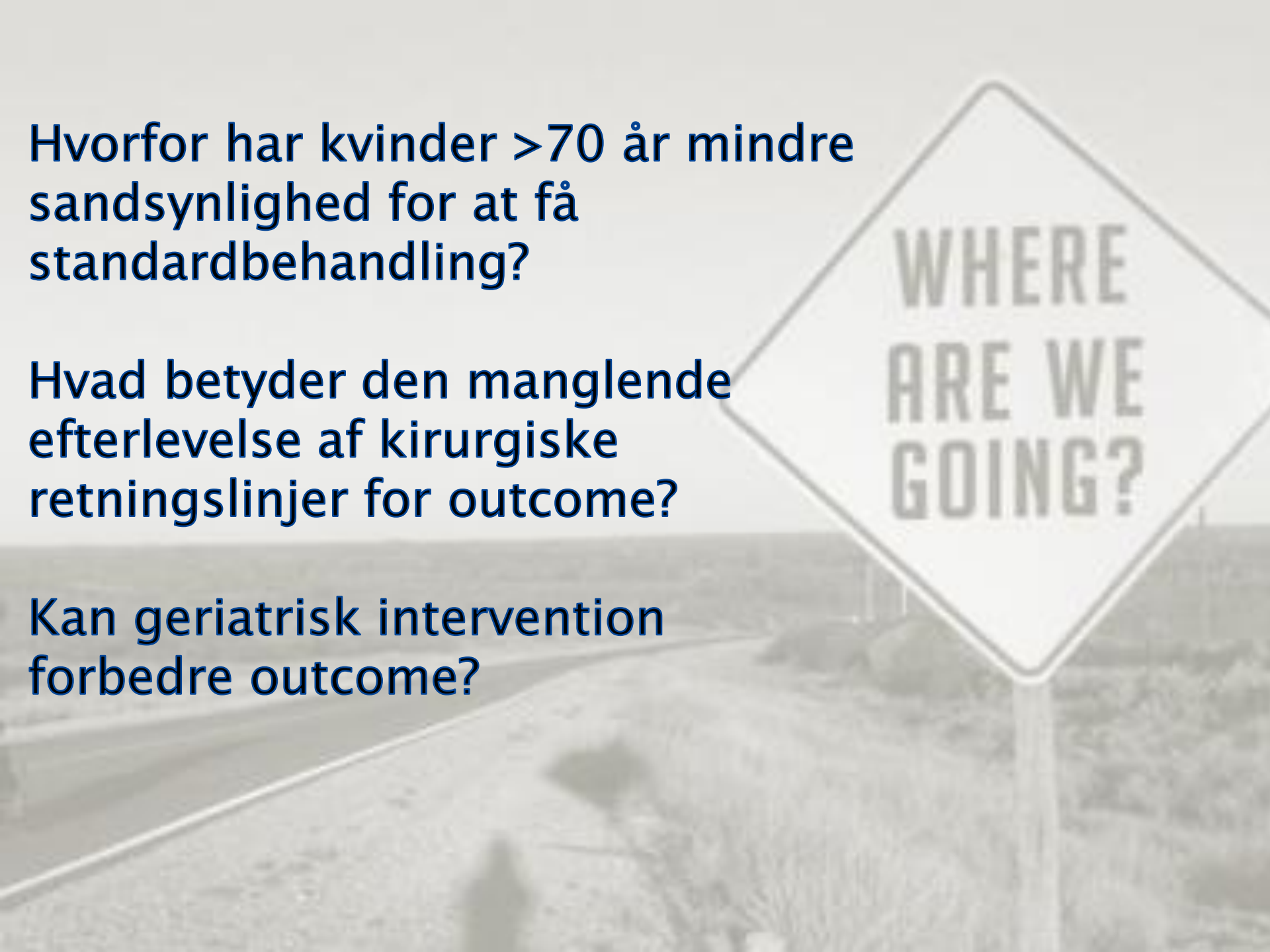
Andre har forgæves forsøgt at reproducere resultaterne

Yu KD *et al* **PLoS One** (2010)

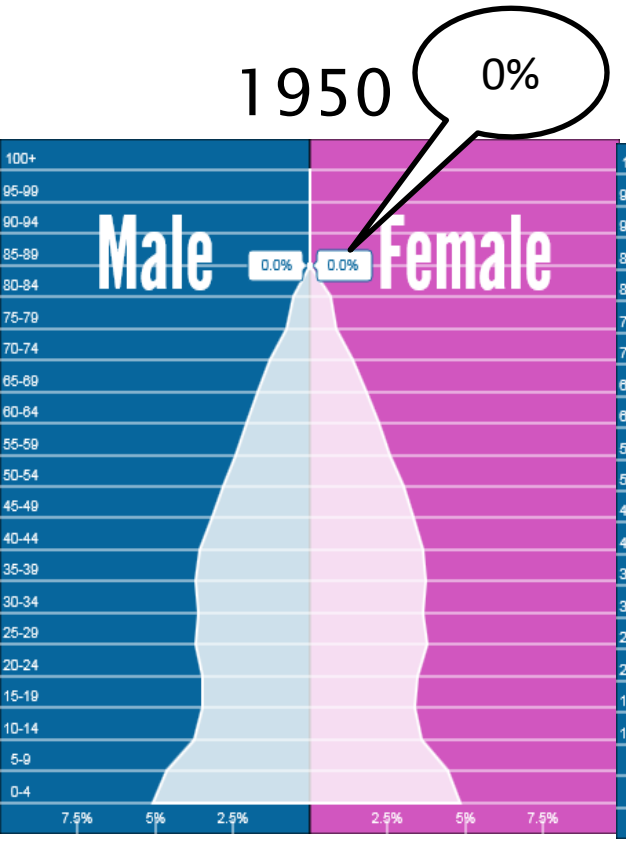
Hvorfor har kvinder >70 år mindre sandsynlighed for at få standardbehandling?

Hvad betyder den manglende efterlevelse af kirurgiske retningslinjer for outcome?

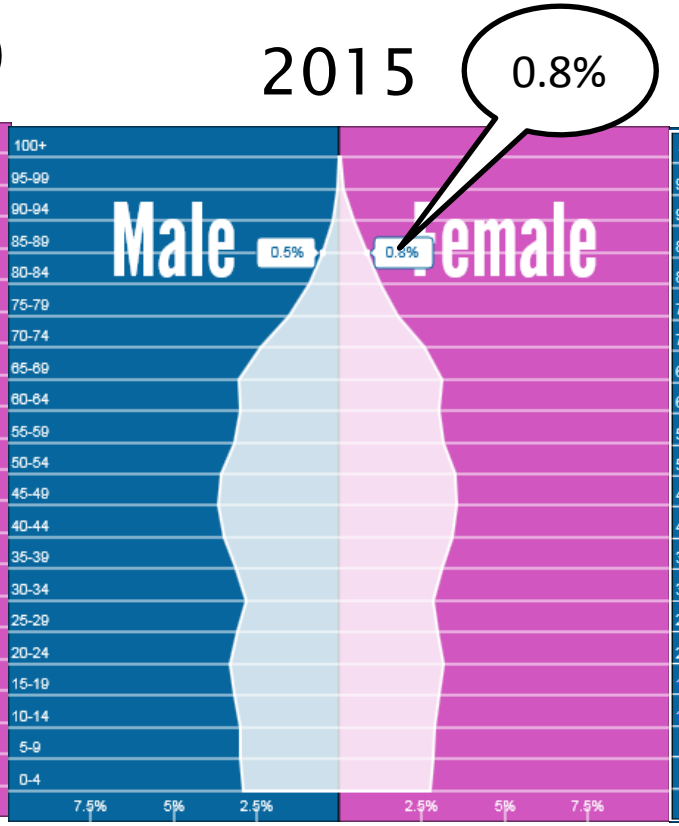
Kan geriatrisk intervention forbedre outcome?



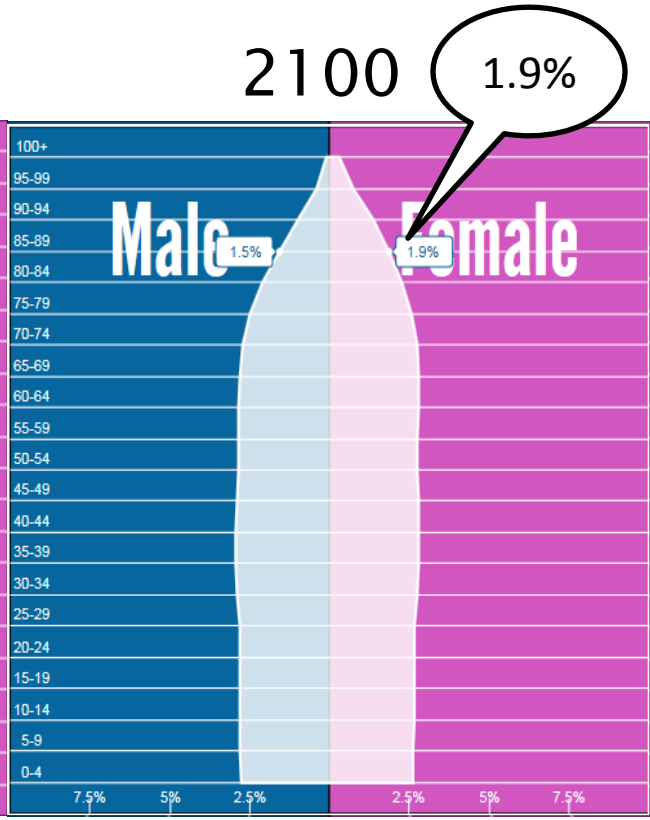
Aldrende befolkning



~4.3 millioner danskere



~5.6 millioner danskere



~ 7 millioner danskere

Martin de Wisser, http://populationpyramid.net/denmark/

Økonomisk støtte

- Helge Peetz og Verner Peetz og hustru Vilma Peetz Legat
- Fru Astrid Thaysens Legat for Lægevidenskabelig Grundforskning
- The Clinical Epidemiological Research Foundation, AUH
- Stipendium, Dept. of Clinical Medicine, AUH

Rejselegater (til Boston Universitet)
- J. William Fulbright Research Scholarship
- Aarhus Universitet
- Kræftens Bekæmpelse
- Fonden af Familien Kjærsgaard, Sunds
- Fabrikant E. Willumsens Mindelegat
- Helga og Peter Kornings Fond
- Lægernes Forsikringsforening af 1891

Timothy L. Lash
Deirdre Cronin-Fenton
Peer Christiansen
Henrik Toft Sørensen

Rebecca Silliman (Boston University)
Thomas Ahern (University of Vermont)

Kollegaer på KEA og Geriatriske Afdelinger (Aarhus og Boston)

The Danish Breast Cancer Cooperative Group co-authors: Niels Kroman, Jens Peter Garne, Anders Bonde Jensen, and Bent Ejlertsen