Standardization of data and analyses

Case-study using cross-Nordic data

Lau Caspar Thygesen

SDU

Institute of Applied Economics & Health Research ApHER

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Finasteride Use and Risk of Male Breast Cancer Using Individual-Level Register Data from Denmark, Finland, and Sweden

Thora M. Kjærulff, Annette K. Ersbøll, Anders Green, Martha Emneus, Klaus Brasso, Peter Iversen, Eero Pukkala, Kristian Bolin and Lau C. Thygesen

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Cancer Medicine

Open Access

ORIGINAL RESEARCH

Finasteride treatment and male breast cancer: a register-based cohort study in four Nordic countries

Mathias Meijer[1,2], Lau Caspar Thygesen[1], Anders Green[3,4], Martha Emneus[3], Klaus Brasso[5], Peter Iversen[5], Eero Pukkala[6,7], Kristian Bolin[8,9], Knut Stavem[10,11,12] & Annette K. Ersbøll[1]

[1]National Institute of Public Health, University of Southern Denmark, Copenhagen, Denmark
[2]Department of Nursing, Metropolitan University College, Copenhagen, Denmark
[3]Institute of Applied Economics and Health Research, Copenhagen, Denmark
[4]Odense Patient Data Explorative Network, Odense University Hospital and University of Southern Denmark, Odense, Denmark
[5]Copenhagen Prostate Cancer Center and Department of Urology, Rigshospitalet, Copenhagen, Denmark
[6]Finnish Cancer Registry, Institute for Statistical and Epidemiological Cancer Research, Helsinki, Finland
[7]School of Health Sciences, University of Tampere, Tampere, Finland
[8]Department of Economics, University of Gothenburg, Gothenburg, Sweden
[9]Centre for Health Economics at the University of Gothenburg, Gothenburg, Sweden
[10]Health Services Research Unit, Akershus University Hospital, Oslo, Norway
[11]Department of Pulmonary Medicine, Medical Division, Akershus University Hospital, Oslo, Norway
[12]Institute of Clinical Medicine, Faculty of Medicine, University of Oslo, Oslo, Norway

Keywords
Breast neoplasms male, finasteride, Nordic countries, pharmacoepidemiology, prostatic

Abstract

A potential link has been suggested between dispensed finasteride and increased

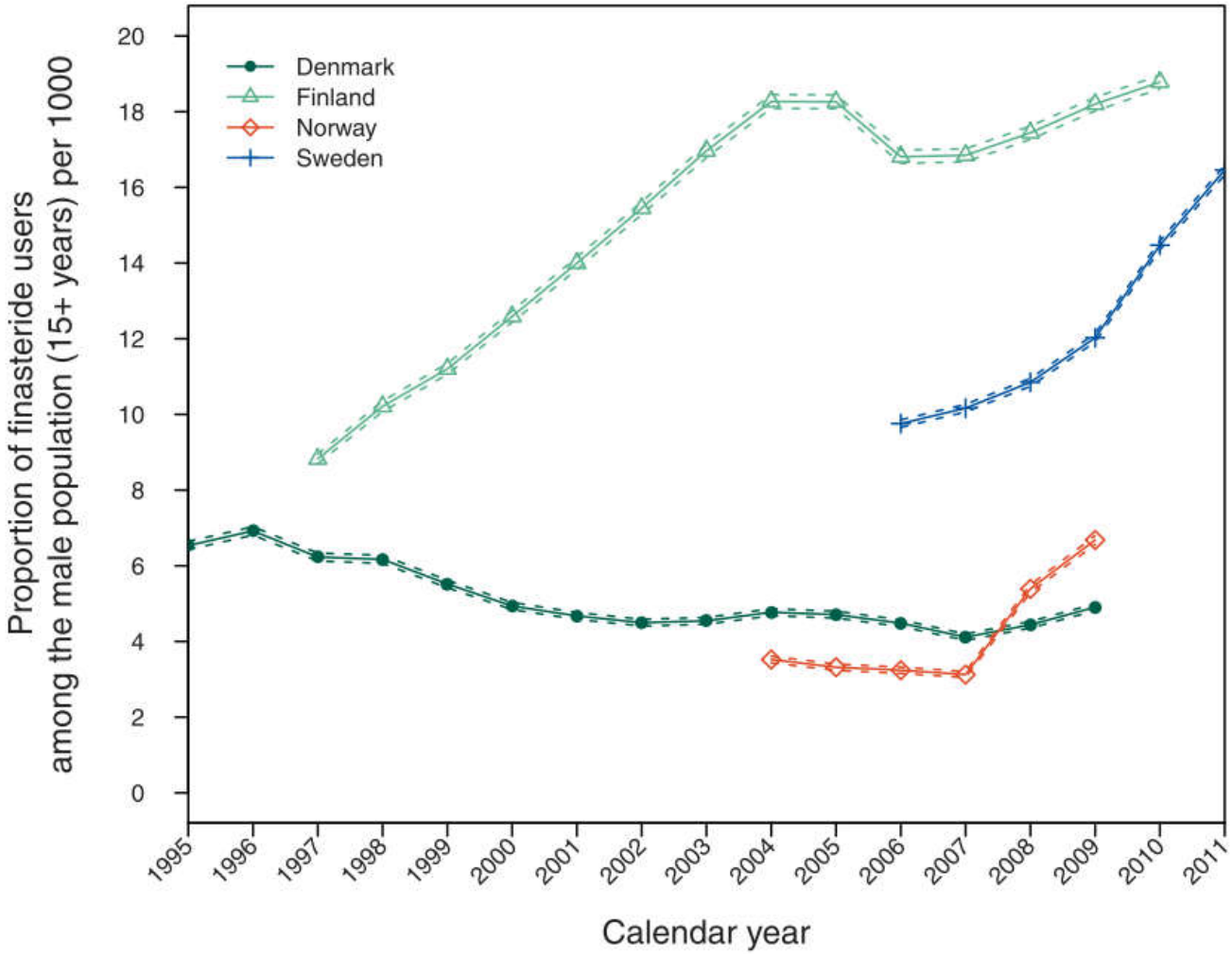
Background

→ Concerns have been raised as to whether finasteride use increases risk of male breast cancer

→ Previous epidemiological evidence conflicting

AIM:

→ Assess if an association between finasteride use and male breast cancer exists after accounting for potential confounders


Denmark
Finland
Norway
Sweden
Proportion of finasteride users among the male population (15+ years) per 1000
0
2
4
6
8
10
12
14
16
18
20
1995
1996
1997
1998
1999
2000
2001
2002
2003
2004
2005
2006
2007
2008
2009
2010
2011
Calendar year

Material

- → The source population consisted of all men (≥35 years)
  - → Denmark (1995–2014)
  - → Finland (1997–2013)
  - → Sweden (2005–2014)
- → Incident male breast cancer in cancer registries
- → Matched with 50 density-sampled, age and country-matched male controls per case
- → Finasteride use derived from prescription registries
- → Potential confounders were identified using the directed acyclic graph methodology and measured by nation-wide registries

Data management Seven steps

1. All national scientific coordinators applied to relevant agencies for permission to perform and access

2. All national scientific coordinators facilitated the construction of the study populations
   - → Sampled via density sampling – same SAS code

3. National scientific coordinators responsible of acquiring and checking the datasets and how registers could be combined
   - → Data control included - but was not restricted to:
     - → Check for legal values for each categorical variable
     - → Check of consistency between dates
     - → Check and advice on the handling of missing data
   - → Data control report
   - → All national coordinators had to agree

Data management
Seven steps

4. The datasets from Finland and Sweden were transferred to Statistics Denmark

5. The Danish scientific coordinator linked the data and the data sets from all countries were joined into a combined analysis dataset

6. The Danish scientific coordinator assessed the data validity of all countries by logical checks, examination of extreme values, and missing data

7. Data analysis and evaluation performed by the Danish scientific coordinator

Variables

Outcome: Male breast cancer (index date)
Exposure: Finasteride use (binary and cumulative)

Numerous potential confounding factors

→ Age
→ Calendar time
→ Diseases
→ Other drugs
→ Occupational exposures
→ Family history of breast cancer
→ Radiation exposure
→ Educational level
→ Living as a single man

Surveillance bias

→ Diagnoses of benign breast disease, gynecomastia and urinary retention
→ Use of drugs that may cause gynecomastia
→ Number of prescriptions, surgeries and hospital contacts
→ Cancer stage
→ Benign prostatic hyperplasia
→ Use of alpha blockers
→ Dutasteride use

Harmonization Diagnostic codes

	ICD7	ICD8	ICD9	ICD10
Denmark	1958-1968	1969–1993	ICD9 never used in Denmark	1994–present
Finland	1952-1968	1969–1986	1987–1995	1996–present
Norway	1958-1968	1969–1985	1986–1995	1996–present
Sweden	1960-1968	1969–1986	1987–1996	1997–present

Harmonization Urbanisation

→Information on the number of persons in the village/city where the men lived (Denmark and Finland)

→In Sweden it was identified as the number of persons in the residential municipality

→In Denmark, urban areas was identified as cities with more than 200 residents

→In Finland the variable was whether the place of residence was in an urban settlement

→In Sweden a urban municipality was identified as one with more than 2000 residents

Harmonization
Missing data

→Educational achievement

→Occupational industries

→Urbanization group

→Diagnoses, healthcare services…

Quality control

→Register-based
→ Data quality therefore difficult to ascertain directly

→Previous studies have evaluated validity of central registers

→These studies in general supported that the validity and completeness are high

→The programming was performed by two researchers independently

→Each national scientific coordinator validated the datasets and explored how the datasets can be combined with the registers

Finasteride use	Cases	Controls	Crude OR (95% CI)[a]	Adjusted OR (95% CI)[b]
Nonuser (<2 redemptions)	967	41,800	1.00 (ref)	1.00 (ref)
User (2+ redemptions)	38	1,258	1.18 (0.84–1.65)	1.09 (0.77–1.54)

Conclusion:

Thoughts on cross-Nordic pharmaco-epidemiology studies

Benefits

→ Rather similar health-care systems and registration systems between Nordic countries
→ Large sample size
→ Population-based studies and real-world data
→ No need to contact individuals
→ No non-response bias (participation, reporting)
→ Valuable time has passed – latency analyses

Limitations / pitfalls

→ Same bias as in all observational studies
→ Data is predetermined
→ Non-comparability (endogeneity)
→ Suboptimal validity
→ Truncation bias
→ Harmonization challenging but possible

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Finasteride

- → Finasteride blocks the conversion of testosterone to the more potent androgen dihydrotestosterone
- → Dihydrotestosterone is the primary androgen contributing to the development of benign prostatic hyperplasia (BPH) and androgenetic alopecia
- → Approved 5 mg for BPH in 1992 and 1 mg for androgenetic alopecia in 1997 by FDA
- → Finasteride 5 mg was approved in March 1993 in Denmark, June 1992 in Finland, and September 1992 in Sweden
- → Finasteride 1 mg was approved in November 1998 in Denmark and Finland and April 1998 in Sweden

Male breast cancer

- → Male breast cancer is a rare disease accounting for 0.6% of all breast cancers
- → Case reports have raised concerns about a potential link between finasteride use and the development of male breast cancer
- → In 2009, a review that 50 cases of male breast cancer have been reported worldwide in association with finasteride 5 mg and three cases in association with finasteride 1 mg
- → Epidemiological studies: Small or selected samples, inadequate confounder adjustment, and have shown conflicting results

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ORIGINAL ARTICLE

Patterns of finasteride use in the male populations of four Nordic countries: A cross-national drug utilization study

T. M. Kjærulff[a], A. K. Ersbøll[a], A. Green[b,c], M. Emneus[c], E. Pukkala[d], K. Bolin[e], K. Stavem[f,g], P. Iversen[h], K. Brasso[h], J. Hallas[i] and L. C. Thygesen[a]

Table 3. Sensitivity analyses with restriction, stratification, alternative definition of the study population, and surveillance factors

		Cases	Controls	Crude odds ratio (95% CI)[a]	Adjusted odds ratio (95% CI)[b]
Combining finasteride and dutasteride	Nonuser	967	41,945	1.00 (ref)	1.00 (ref)
	User	42	1,604	1.02 (0.74–1.41)	0.95 (0.68–1.32)
Only persons ≥65 years	Nonuser	575	23,260	1.00 (ref)	1.00 (ref)
	User	33	1,122	1.12 (0.78–1.61)	1.02 (0.70–1.48)
With 2-year lag period	Nonuser	983	42,186	1.00 (ref)	1.00 (ref)
	User	22	872	0.96 (0.62–1.49)	0.88 (0.56–1.37)
Only Denmark and Finland	Nonuser	650	28,812	1.00 (ref)	1.00 (ref)
	User	30	934	1.30 (0.89–1.91)	1.20 (0.81–1.78)
Including finasteride use in the first 6 months of registration	Nonuser	970	42,512	1.00 (ref)	1.00 (ref)
	User	53	1,705	1.23 (0.92–1.65)	1.15 (0.86–1.55)
Surveillance factors					
Hospital contacts					
Below mean	Nonuser	415	23,274	1.00 (ref)	1.00 (ref)
	User	10	332	1.64 (0.84–3.19)	1.64 (0.84–3.21)
Above mean	Nonuser	552	18,526	1.00 (ref)	1.00 (ref)
	User	28	926	0.99 (0.67–1.48)	0.94 (0.63–1.41)
Prescription redemptions					
Below mean	Nonuser	469	21,530	1.00 (ref)	1.00 (ref)
	User	6	161	1.76 (0.75–4.15)	1.78 (0.74–4.25)
Above mean	Nonuser	498	20,270	1.00 (ref)	1.00 (ref)
	User	32	1,097	1.15 (0.79–1.67)	1.03 (0.71–1.51)
Cancer stage[c]					
Localized	Nonuser	437	18,856	1.00 (ref)	1.00 (ref)
	User	19	572	1.30 (0.81–2.10)	1.13 (0.69–1.84)
Regional/metastatic	Nonuser	428	18,612	1.00 (ref)	1.00 (ref)
	User	17	588	1.12 (0.67–1.86)	1.19 (0.71–2.00)

[a]Matched by age and country. Conditional logistic regression.

[b]Matched by age and country and adjusted for benign prostatic hyperplasia, exogenous testosterone, educational level, testicular disorders, and urban/rural differences. Conditional logistic regression.

[c]104 cases (10.4%) had no information on cancer stage and were therefore excluded from this analysis as were their corresponding 4,430 controls.

Study or Subgroup	log[Risk Ratio]	SE	Weight	IV, Random, 95% CI	Year
Bird 2013	−0.3567	0.37	11.4%	0.70 [0.34–1.45]	2013
Duijnhoven 2014	0.077	0.281	19.7%	1.08 [0.62–1.87]	2014
Robinson 2015	−0.4308	0.36	12.0%	0.65 [0.32–1.32]	2015
Hagberg 2017	0.4187	0.467	7.1%	1.52 [0.61–3.80]	2017
Kjærulff (this study)	0.0862	0.177	49.7%	1.09 [0.77–1.54]	2018
Total (95% CI)			**100.0%**	**1.00 [0.78–1.27]**	

Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 3.48$, df = 4 ($P = 0.48$); $I^2 = 0\%$

Test for overall effect: $Z = 0.04$ ($P = 0.97$)