Use of drug register data in Swedish cancer studies

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Outline

- About the Swedish Prescribed Drug Register

- Examples record-linkage studies:
- Drug utilization: adherence, patterns of use before and after a cancer diagnosis

- Drug induced side effects

The Swedish Prescribed Drug Register

- Start July 1, 2005
- Source population: 9.5 million
- Updated monthly

The Swedish Prescribed Drug Register Contents:

- **Patient details**
- **Dispensation details**
- Costs
- Prescriber details
- Pharmacy
- **Drug details**

Patient details

- Unique personal identifier
- Age
- Sex
- County of residence

Dispensation details

- Prescription date
- Date of dispensation
- Number of dispensed units

- Free text: from prescription

Drug details

- ATC-code
- Generic name
- Brand name
- DDD per package
- Package size
- Strength/dosage
- Type
- Unique drug ID according to Swedish Medical Products Agency

Pharmacoepi studies to date

- 61 Swedish studies identified in recent review
- Main focus: drug utilization

- Majority on cardiovascular and nervous system diseases

- Few cancer studies, to date mainly based on data from the Swedish National Cancer Register

FULL PAPER

BJC

British Journal of Cancer (2013), 1–5 | doi: 10.1038/bjc.2013.411

Keywords: low-dose aspirin; tumour-stage characteristics; anti-platelet therapy

Low-dose aspirin use and cancer characteristics: a population-based cohort study

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Background: Long-term daily use of aspirin has been associated with reduced cancer mortality. To explore this association, we compared tumour TNM characteristics among aspirin users with those among non-users.

Methods: From the Swedish Cancer Register, we identified patients diagnosed with colorectal, lung, prostate and breast cancers between 2006 and 2009 and matched them to the Swedish Prescribed Drug Register to obtain information on low-dose aspirin use prior to diagnosis. Contingency table and logistic regression analyses were used to test for association and obtain odds ratios (ORs).

Results: We identified 17 041 colorectal, 9766 lung, 29 770 prostate and 20 299 breast cancer patients. The proportion of low-dose aspirin users was ~26% among colorectal, lung and prostate cancer patients and ~14% among breast cancer patients. Adjusted for age, gender, education level and place of residence, low-dose aspirin use was associated with lower tumour extent (T) for colorectal and lung cancers ($P<0.0001$) but not for prostate and breast cancers. The adjusted OR of aspirin use for the T4 vs T1 categories was ~0.7 (95% confidence interval (CI) 0.6–0.8). For all cancers, we found no evidence of association of aspirin use with nodal involvement (N). Except for a borderline result in prostate cancer (OR ~0.9; 95% CI 0.8–1.0), aspirin use was associated with a lower rate of metastatic disease (ORs ~0.6–0.8). Among the histological subgroups of lung cancer, significant differences in tumour extent were observed most clearly within the adenocarcinoma subgroup (OR ~0.6, 95% CI 0.5–0.8), although numbers of other subtypes were more limited; and there was a significant reduction of ~20–30% in the odds of metastasis among the aspirin users across the subgroups.

Conclusion: Use of low-dose aspirin in the year prior to diagnosis was found to be associated with lower tumour extent and fewer metastatic disease for colorectal and lung cancers. For these cancers, the benefit of aspirin use appears to be during both early and late cancer progression.

Numerous studies, observational as well as randomised, have been performed to assess the association between aspirin intake and cancer risk and mortality. Evidence is growing that daily aspirin intake for 5 years or longer reduces the risk of death of cancer for several common cancers, notably colorectal and lung (Rothwell *et al*, 2011). This mortality benefit may partially be explained by reduced risk. Notably, however, Women's Health Study (Cook *et al*, 2005), a randomised study of ~40 000 participants, did not show benefit of aspirin *vs* placebo for cancer risk reduction. An earlier study from the Nurses' Health Study cohort also reported null effects of aspirin on breast cancer risk (Egan *et al*, 1996). Reduced risk of colorectal cancer (Rothwell *et al*, 2010; Rothwell *et al*, 2012) was established in a meta-analysis of randomised studies, where both low-dose (75–300 mg daily) and high-dose aspirin (≥500 mg daily) were attributed positive effects, primarily for long-term intake. Thus, so far convincing findings

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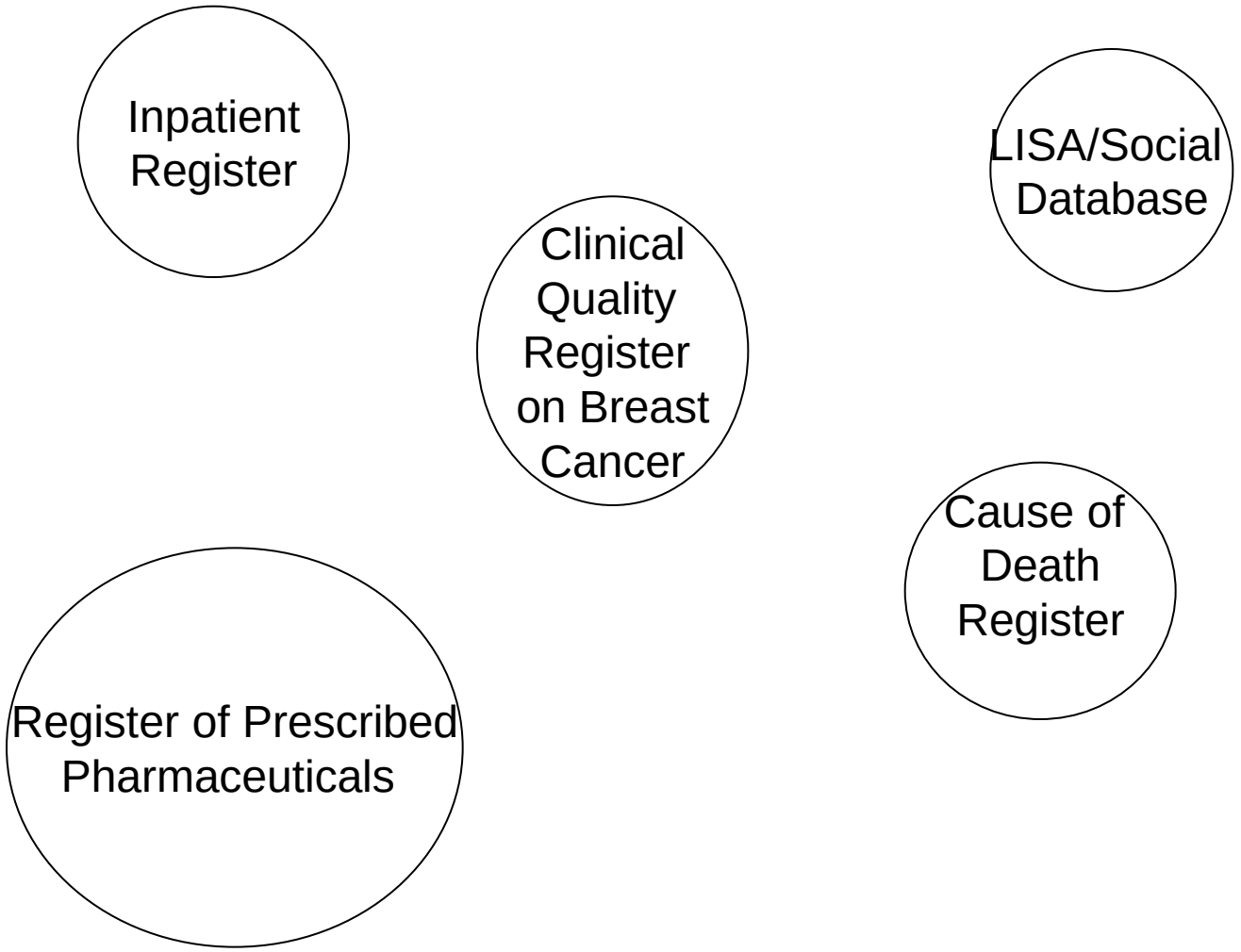
Revised 18 June 2013; accepted 24 June 2013

Clinical Cancer Registers

- Includes data on diagnostic intensity, tumor characteristics and intended treatment
- Completeness: 95 % percent compared to the National Cancer Register to which reporting is mandated by law
- Record linkages to Prescibed Drug Register


Inpatient Register
LISA/Social Database
Clinical Quality Register on Breast Cancer
Cause of Death Register
Register of Prescribed Pharmaceuticals

Breast Cancer Res Treat
DOI 10.1007/s10549-012-1961-4

EPIDEMIOLOGY

Adherence and discontinuation of adjuvant hormonal therapy in breast cancer patients: a population-based study

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Received: 7 October 2011 / Accepted: 16 January 2012

Abstract Adherence to long-term pharmacological treatment for chronic conditions is often less than optimal. Till date, a limited number of population-based studies have assessed adherence to adjuvant hormonal therapy in breast cancer, a therapy with proven benefits in terms of reductions of recurrence and mortality. We aimed to examine rates of adherence and early discontinuation in Sweden where prescribed medications are subsidized for all residents and made available at reduced out-of-pocket costs. Individual-level data were obtained from Regional Clinical Quality Breast Cancer Registers, the Swedish Prescribed Drug Register, and several other population-based registers. Multivariate logistic regression was used to analyze factors associated with adherence to prescribed medication for a period of 3 years. Between January 1 and December 31, 2005, 1,741 patients in central Sweden were identified with estrogen receptor positive breast cancer, and at least one prescription dispensation of either tamoxifen or an aromatase inhibitor. Of these women, 1,193 (69%) were fully

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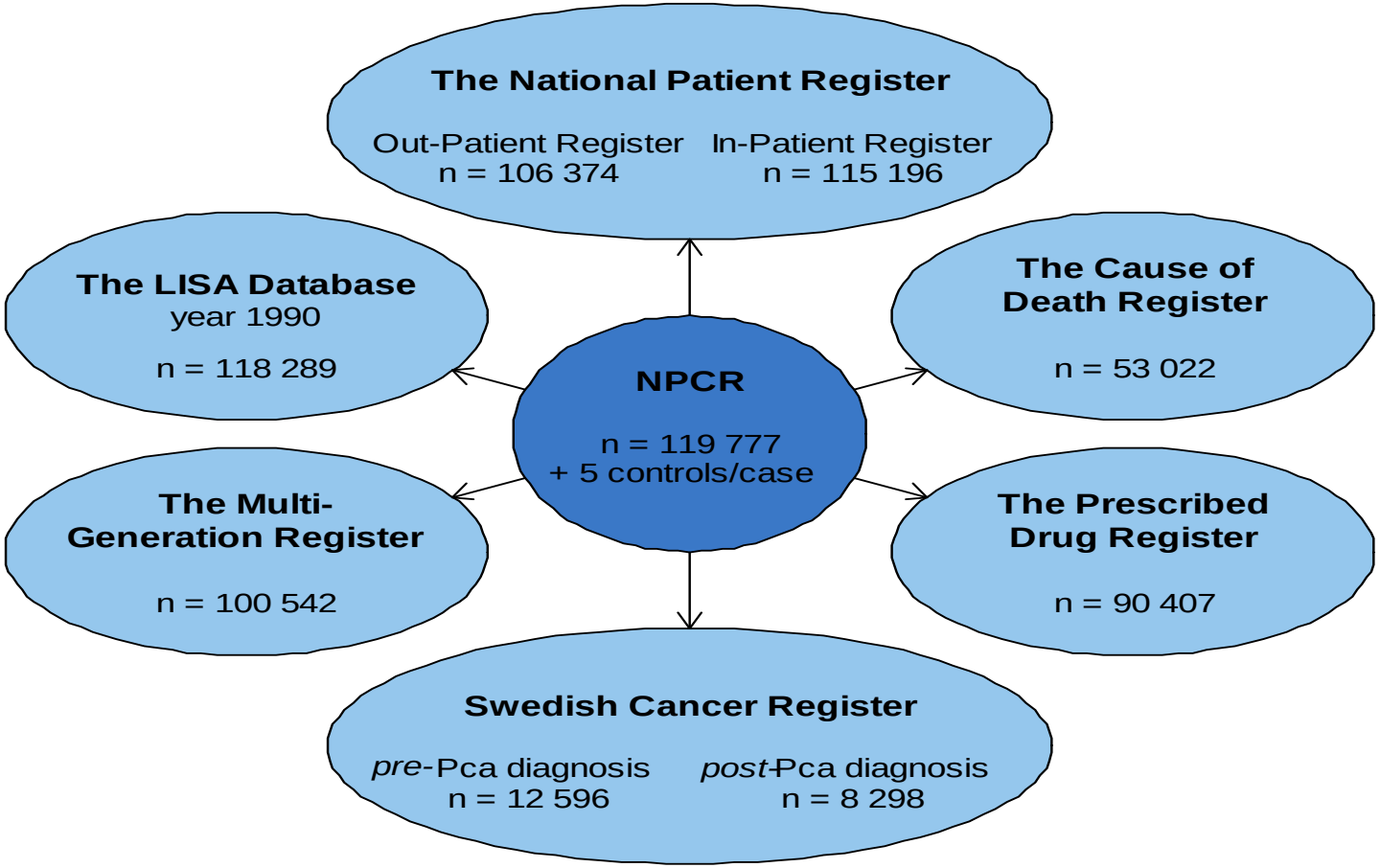
PCBaSe Sweden 2.0



Ongoing projects

- Patterns of fillings over time before and after a cancer diagnosis as a proxy of quality of life

- Project 1: drugs for erectile dysfunction in relation to a prostate cancer diagnosis

- Project 2: sedatives, hypnotics, antidepressants, pain killers in men with prostate cancer

Further example PCBaSe 2.0

- Study on drug induced side effects

Two randomised trials have shown a decreased risk of prostate cancer overall in men on 5-ARI - finasteride

- Prostate Cancer Prevention trial (PCPT)
- Reduction by Dutasteride of Prostate Cancer Events (REDUCE) trial.

In both these trials, there was also an increased risk of cancer with Gleason scores 8-10

BMJ

BMJ 2013;346:f3406 doi: 10.1136/bmj.f3406 (Published 18 June 2013)

RESEARCH

Use of 5α-reductase inhibitors for lower urinary tract symptoms and risk of prostate cancer in Swedish men: nationwide, population based case-control study

OPEN ACCESS

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Abstract

Objective To assess the association between 5α-reductase inhibitor (5-ARI) use in men with lower urinary tract symptoms and prostate cancer risk.

Design Nationwide, population based case-control study for men diagnosed with prostate cancer in 2007-09 within the Prostate Cancer data Base Sweden 2.0.

Setting The National Prostate Cancer Register, National Patient Register, census, and Prescribed Drug Register in Sweden, from which we obtained data on 5-ARI use before date of prostate cancer diagnosis.

Participants 26 735 cases and 133 671 matched controls; five controls per case were randomly selected from matched men in the background population. 7515 men (1499 cases and 6016 controls) had been exposed to 5-ARI. 412 men had been exposed to 5-ARI before the diagnosis of a cancer with Gleason score 8-10.

Main outcome measures Risk of prostate cancer calculated as odds ratios and 95% confidence intervals by conditional logistic regression analyses.

Results Risk of prostate cancer overall decreased with an increasing duration of exposure; men on 5-ARI treatment for more than three years had an odds ratio of 0.72 (95% confidence interval 0.59 to 0.89; P<0.001 for trend). The same pattern was seen for cancers with Gleason scores 2-6 and score 7 (both P<0.001 for trend). By contrast, the risk of tumours with Gleason scores 8-10 did not decrease with increasing exposure time to 5-ARI (for 0-1 year of exposure, odds ratio 0.96 (95% confidence interval 0.83 to 1.11); for 1-2 years, 1.07 (0.88 to 1.31); for 2-3 years, 0.96 (0.72 to 1.27); for >3 years, 1.23 (0.90 to 1.68); P=0.46 for trend).

Conclusions Men treated with 5-ARI for lower urinary tract symptoms had a decreased risk of cancer with Gleason scores 2-7, and showed no evidence of an increased risk of cancer with Gleason scores 8-10 after up to four years' treatment.

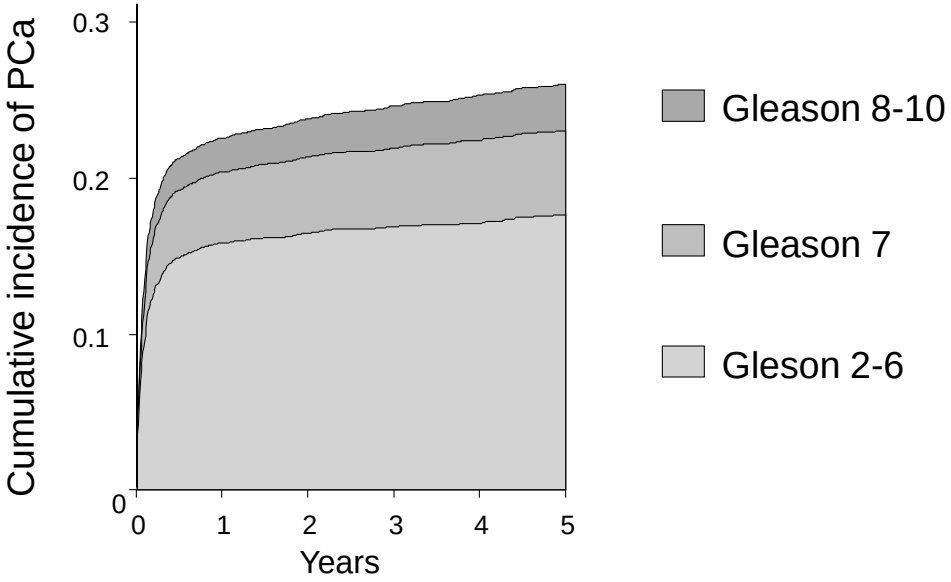
Introduction

Chemoprevention by use of 5α-reductase inhibitors (5-ARI) to decrease risk of prostate cancer has been investigated in two large randomised clinical trials. Both these trials showed a decreased risk of prostate cancer overall in men on 5-ARI—finasteride in the Prostate Cancer Prevention trial (PCPT) and dutasteride in Reduction by Dutasteride of Prostate Cancer Events (REDUCE) trial.[1 2] These 5-ARIs inhibit the conversion of testosterone to dihydrotestosterone, the most potent androgen in the prostate, and thereby decrease androgen receptor activity.[3] There was a 23-25% reduction in risk of prostate cancer at biopsy for men receiving 5-ARI, compared with men receiving placebo, in both trials. However, in both trials, there was also an increased risk of cancer with Gleason scores 8-10. Based on these findings, The US Food and Drug Administration (FDA) issued a safety announcement in 2011, stating that "5 alpha reductase inhibitors may increase the risk of a more serious form of prostate cancer."[4]

The reason for the observed increase in risk in these trials has not been conclusively elucidated, with different explanations for these associations put forward.[5-7] One theory is that the increase is real and that 5-ARI promotes prostate cancer with Gleason scores 8-10, possibly mediated through lower concentrations of 3β-Adiol and resulting in a decreased stimulation of the oestrogen β receptor.[8] Another theory is that the association is spurious and caused by detection bias, because 5-ARI facilitates the detection of small foci of tumours with Gleason scores 8-10.[9] To what degree these Gleason 8-10

Cohort
or
Case-control study?

Cohort approach

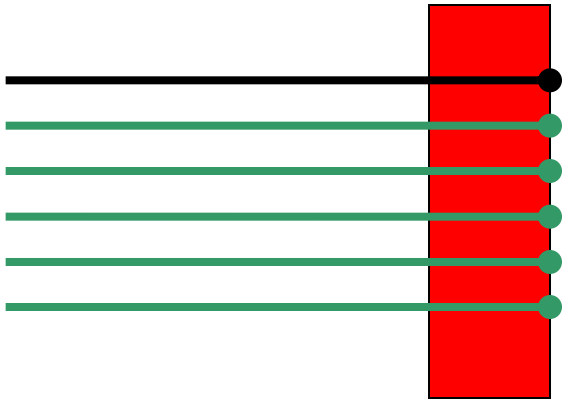


Time since first prescription
of 5α-reductase inhibitors

Problems

- 5α-reductase inhibitors is used as a diagnostic tool
- Exposure calculation (ΣDDD or calendar time)
- Comparison group?

Case-control approach

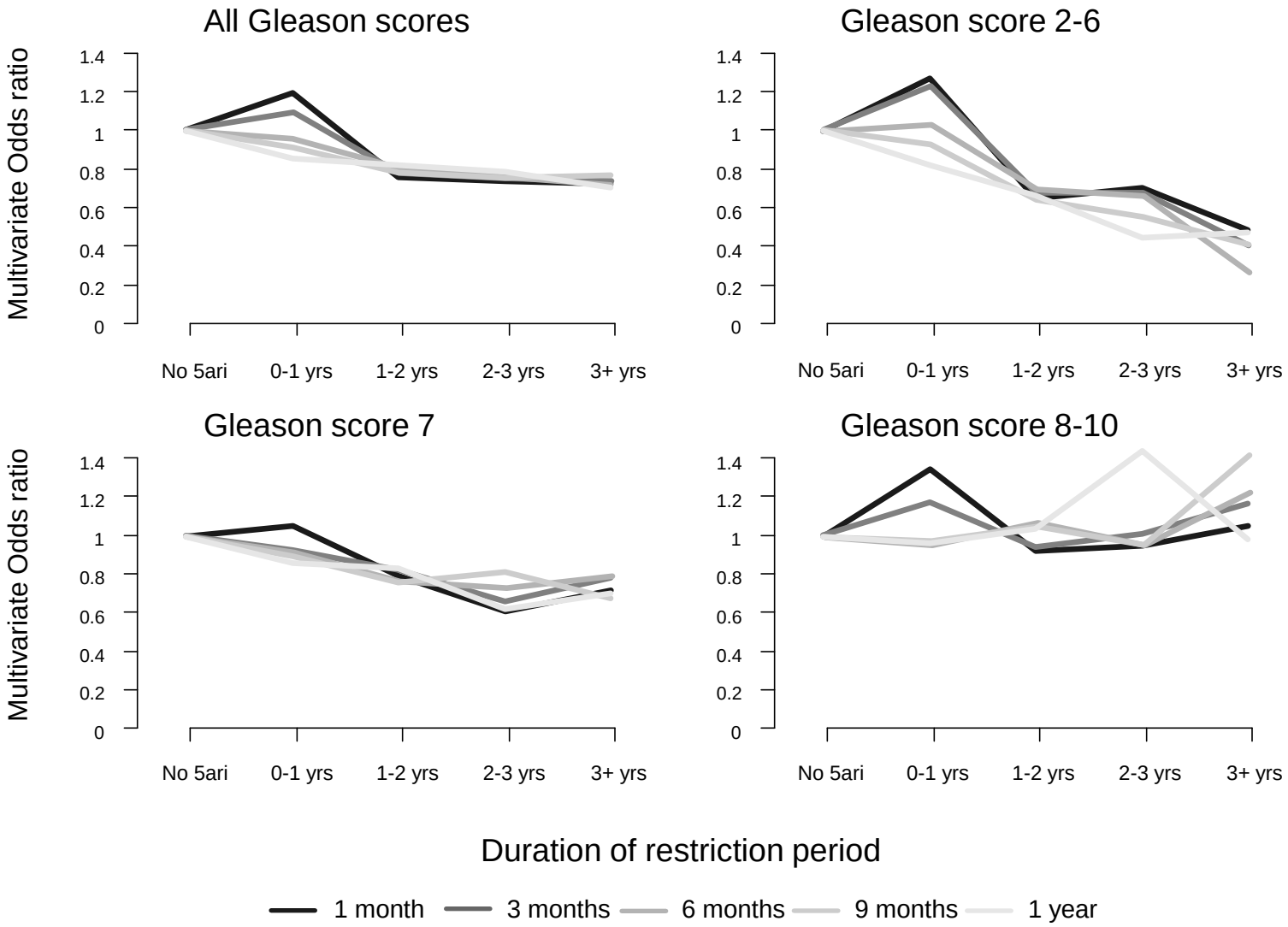


Restriction period

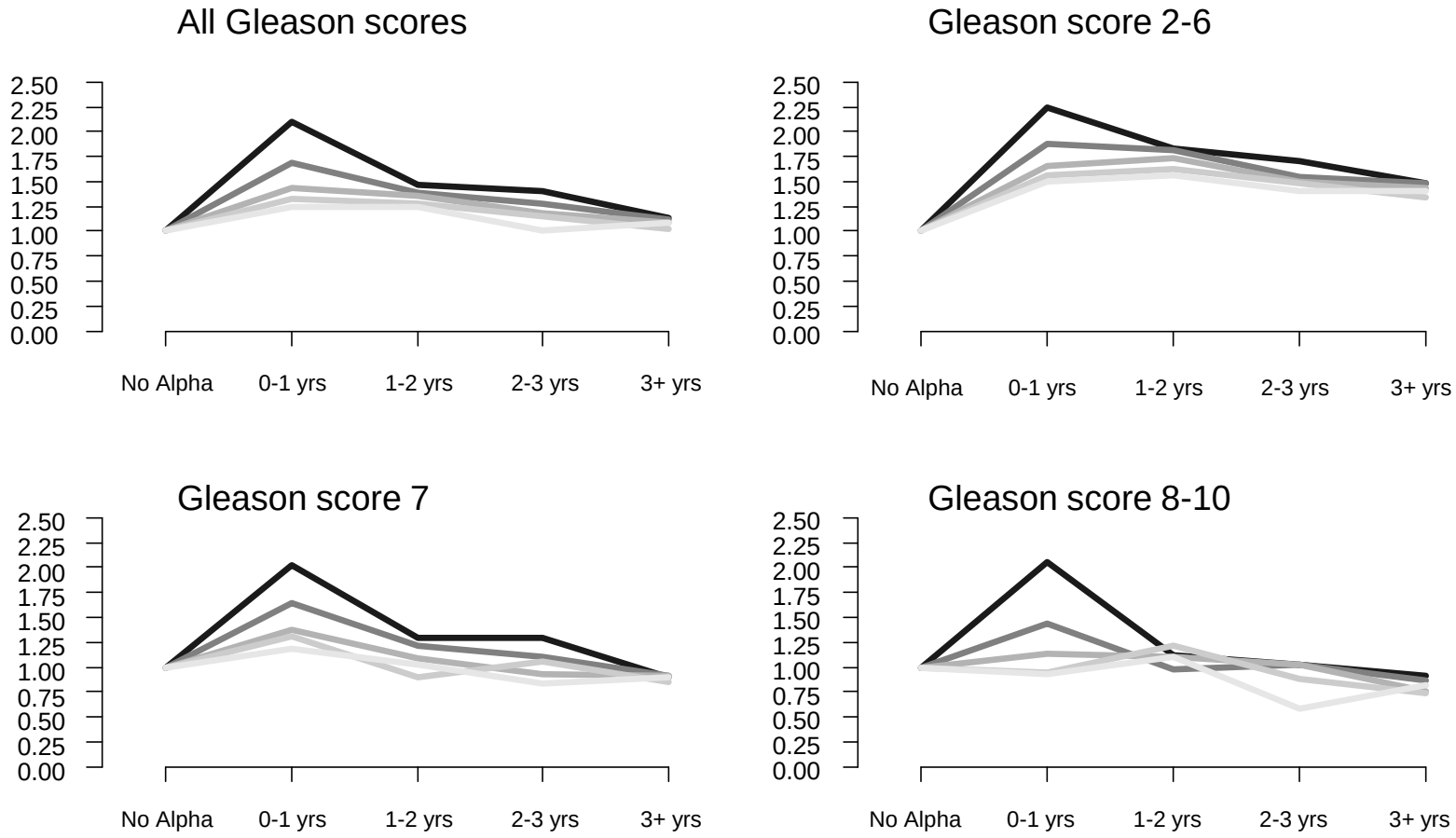
During the restriction period exposure to
- 5-ARI,
- α blockers,
- transurethral resection of the prostate (TURP)
- prostate biopsies

was ignored

5α-reductase inhibitors



α-blockers


All Gleason scores
Gleason score 2-6
Gleason score 7
Gleason score 8-10
2.50
2.25
2.00
1.75
1.50
1.25
1.00
0.75
0.50
0.25
0.00
No Alpha
0-1 yrs
1-2 yrs
2-3 yrs
3+ yrs
Duration of restriction period
1 month
3 months
6 months
9 months
1 year

Sweden: summary

- ”Young” register
- Weaknesses: absence of systematic information on indication, and drugs dispensed in-hospital
- Strengths: nation-wide, truly population based
- To date under utilized in cancer studies
- Future potential in a variety of applications

- Thank you for your attention

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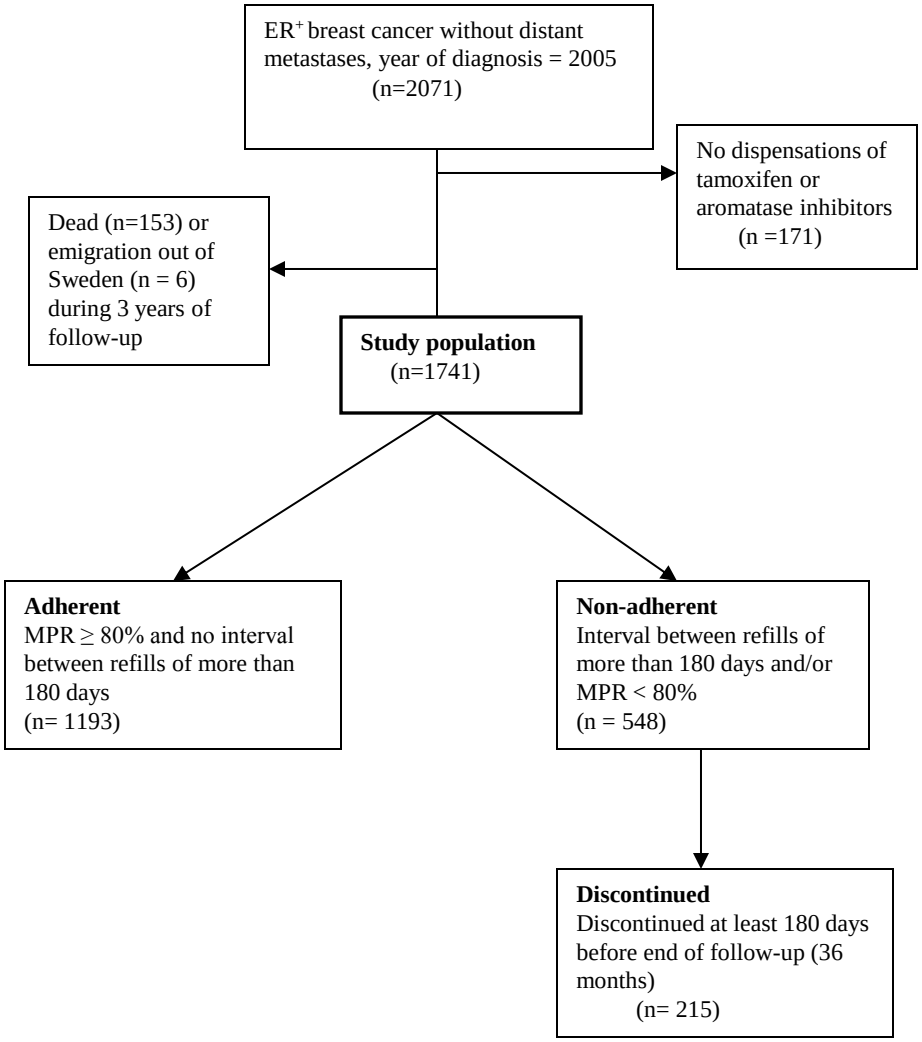
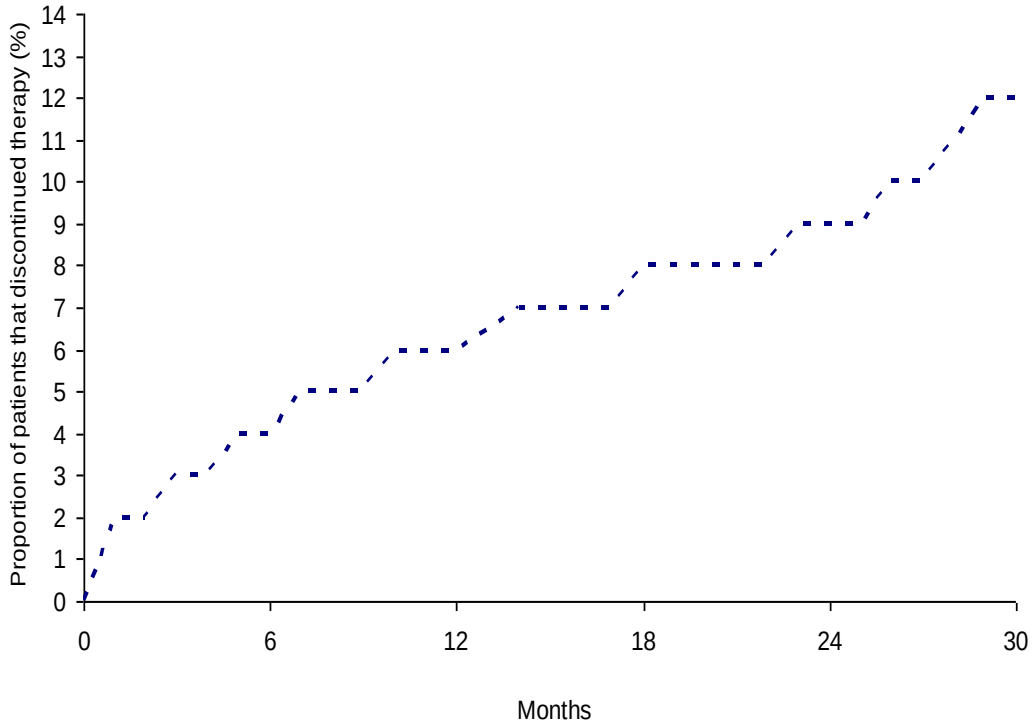

ER+ breast cancer without distant metastases, year of diagnosis = 2005
(n=2071)
No dispensations of tamoxifen or aromatase inhibitors
(n =171)
Dead (n=153) or emigration out of Sweden (n = 6) during 3 years of follow-up
Study population
(n=1741)
Adherent
MPR ≥ 80% and no interval between refills of more than 180 days
(n= 1193)
Non-adherent
Interval between refills of more than 180 days and/or MPR < 80%
(n = 548)
Discontinued
Discontinued at least 180 days before end of follow-up (36 months)
(n= 215)


Proportion of patients that discontinued therapy (%)
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
0
6
12
18
24
30
Months

5α-reductase inhibitors for lower urinary tract symptoms and risk of prostate cancer