Post-diagnosis NSAID use and risk of contralateral breast cancer

a Danish nationwide cohort study

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Background: NSAIDs

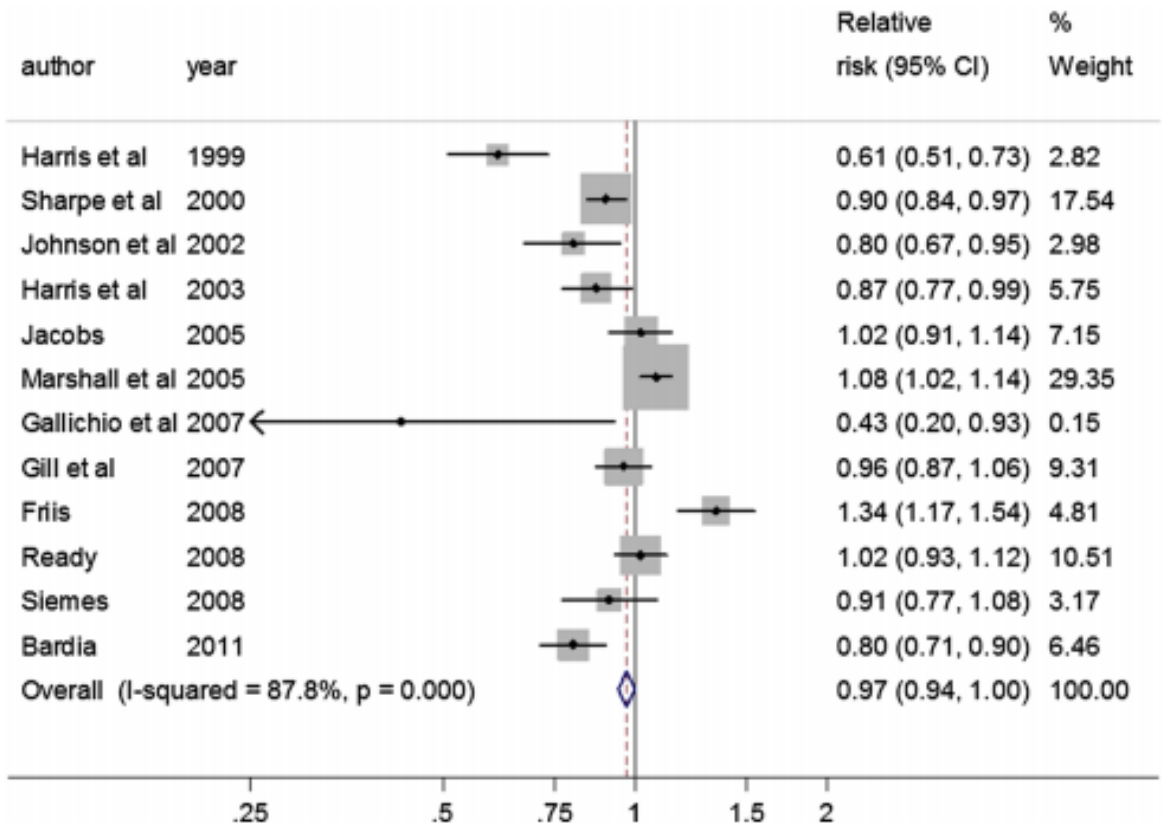
- Inhibition of the COX-1 and COX-2 enzymes
- Aspirin, non-selective NSAIDs and COX-2 inhibitors
- Analgesic
  Anti-inflammatory
  Anti-neoplastic?
- *In vitro* and *In vivo*: inhibition of proliferation of breast tumor cells, induction of apoptosis and suppression of tumor growth.

Background: NSAIDs and breast cancer risk

- NSAID use and breast cancer risk: *cohort studies*

Studies included in the meta-analysis:

- NSAIDs differ in COX-2 selectivity
- Self reported versus prescription-based
- Carried out in the general population



de Pedro et al. (2015)

The occurrence of **contralateral breast cancer (CBC)** may serve as a useful **high-risk model** to identify preventive drug effects.

Study design: nationwide cohort study

Study population

Danish Breast Cancer Cooperative Group (DBCG) database

All women aged >20 years with an incident diagnosis of unilateral breast cancer (stage I-III) during 1996-2012

No history of cancer

N = 52,723

DBCG DANISH BREAST CANCER GROUP

Outcome: CBC

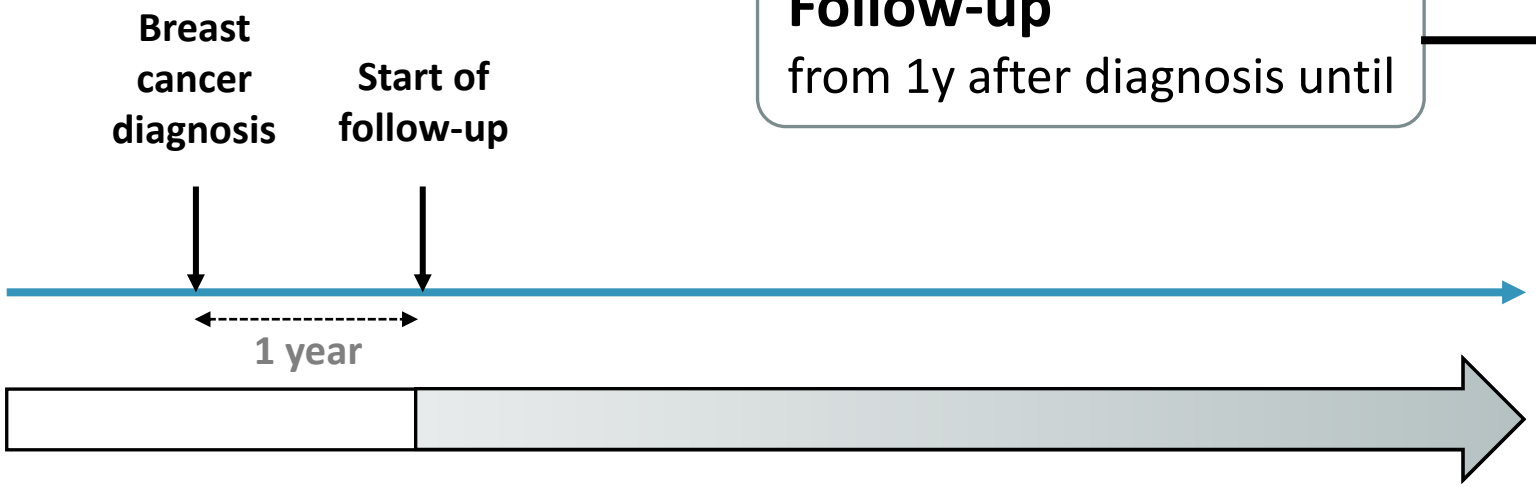
Contralateral breast cancer database (outcome)

N = 1,382

Data sources

Danish nationwide registries (linkage by CPR-number)

Study design: nationwide cohort study



Follow-up
from 1y after diagnosis until

Outcome of interest
- Contralateral breast cancer

Censoring outcomes
- Ipsilateral breast cancer
- Distal disease at CBC diagnosis
- Other malignancies
- Death
- Emigration
- Mastectomy of the contralateral breast
- End of follow-up (December 2013)

Post-diagnosis NSAID use
≥2 prescriptions after breast cancer diagnosis lagged by 1 year.

Cox regression: time-varying

Post-diagnosis use	Person-years	CBC	Age-adjusted HR (95% CI)	Fully adjusted HR (95% CI)
Low-dose aspirin				
Non-use	268,935	1,214	Reference	Reference
Ever use	41,602	168	0.87 (0.73-1.03)	0.89 (0.74-1.08)
Non-aspirin NSAIDs				
Non-use	215,788	937	Reference	Reference
Ever use	94,748	445	0.99 (0.87-1.11)	0.99 (0.87-1.12)
COX-2 selectivity				
Non-selective NSAIDs	40,723	185	0.96 (0.82-1.13)	0.97 (0.83-1.14)
COX-2 selective NSAIDs	26,404	130	1.05 (0.87-1.27)	1.04 (0.86-1.26)
Mixed	27,622	130	0.96 (0.79-1.16)	0.96 (0.79-1.16)

No apparent differences in HRs according to different patterns of use: consistency, duration, intensity.

Competing risks

Censoring outcomes

- **Death**
- Other malignancies
- Mastectomy of the contralateral breast
- Ipsilateral breast cancer
- Distal disease at CBC diagnosis
- Emigration
- End of follow-up

→ **1,382 CBCs versus 15,401 competing events (n = 52,723)**

Breast cancer patients who are censored are likely to have a different underlying risk of CBC then those remaining in the cohort.

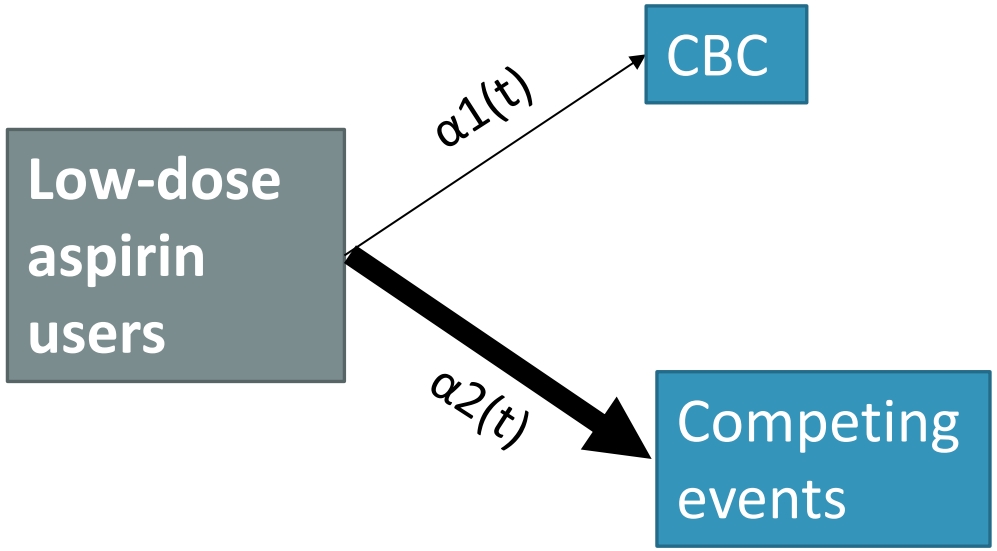
→ censoring was **NOT non-informative** in our study

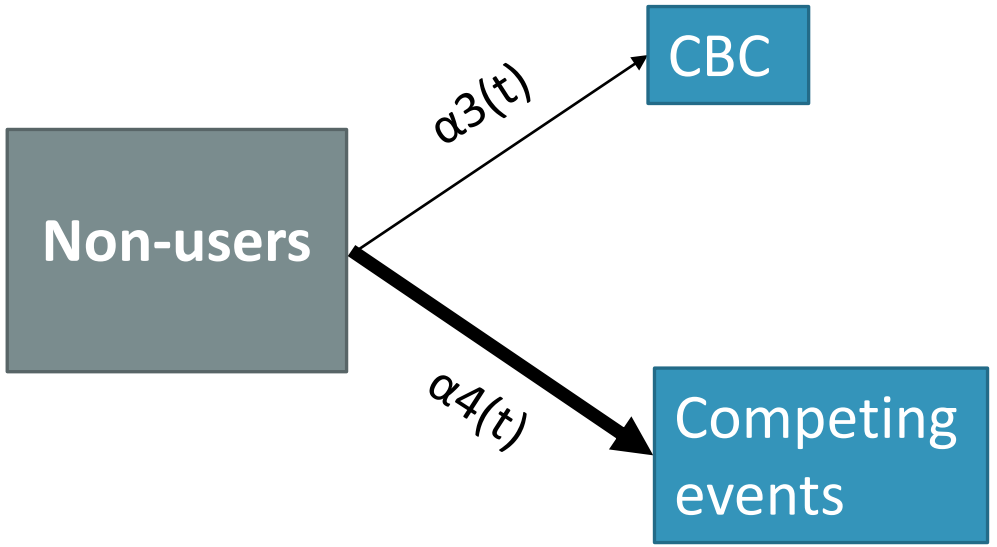
Cox-regression: time-varying

Post-diagnosis use	Person-years	CBC	Age-adjusted HR (95% CI)	Fully adjusted HR (95% CI)	Competing events	Age-adjusted HR (95% CI)	Fully adjusted HR (95% CI)
Low-dose aspirin							
Non-use	268,935	1,214	Reference	Reference	11819	Reference	Reference
Ever use	41,602	168	0.87 (0.73-1.03)	0.89 (0.74-1.08)	3582	1.29 (1.24-1.34)	1.19 (1.14-1.24)

Thus, the slightly decreased HR for CBC among low-dose aspirin users may partly be explained by competing events.

Cox regression





$$HR_{CBC} = \frac{\alpha 1(t)}{\alpha 3(t)} = 0.89$$

$$HR_{comp.events} = \frac{\alpha 2(t)}{\alpha 4(t)} = 1.19$$

Fine and Gray: subdistribution model

$$SHR_{CBC} = \frac{\lambda 1(t)}{\lambda 2(t)} = 0.95 \quad (95\%\ CI: 0.79\text{-}1.15)$$

- Breast cancer patients who experience a competing event remain in the risk set.
  → although they are in fact no longer at risk of developing CBC.
- Allows interpretation of the estimate as a risk

Strengths

- Nationwide
- Clinical database – high case validity
- Use of high quality, demographic and health registries
- Complete follow-up

Limitations

- Over-the-counter drug use
- Residual confounding
- Compliance to NSAID therapy
- Rare outcome

Conclusion

No clear evidence for a protective effect of post-diagnosis NSAID use on CBC risk.

Collaborators

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