Post-diagnosis NSAID use and risk of contralateral breast cancer
a Danish nationwide cohort study

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⁵ Department of Oncology, Rigshospitalet, Copenhagen, Denmark.
⁶ Department of Breast Surgery, Rigshospitalet, Copenhagen, Denmark.
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

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

\[N = 52,723\]

**Outcome: CBC**
Contralateral breast cancer database (outcome)

\[N = 1,382\]

**Data sources**
Danish nationwide registries (linkage by CPR-number)
Study design: nationwide cohort study

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.

Breast cancer diagnosis

Start of follow-up

Follow-up from 1y after diagnosis until

1 year

End of follow-up (December 2013)
Cox regression: time-varying

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

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

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<th>Post-diagnosis use</th>
<th>Person-years</th>
<th>CBC</th>
<th>Age-adjusted HR (95% CI)</th>
<th>Fully adjusted HR (95% CI)</th>
<th>Competing events</th>
<th>Age-adjusted HR (95% CI)</th>
<th>Fully adjusted HR (95% CI)</th>
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<td>Reference</td>
<td>Reference</td>
<td>11819</td>
<td>Reference</td>
<td>Reference</td>
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<tr>
<td>Ever use</td>
<td>41,602</td>
<td>168</td>
<td>0.87 (0.73-1.03)</td>
<td>0.89 (0.74-1.08)</td>
<td>3582</td>
<td>1.29 (1.24-1.34)</td>
<td>1.19 (1.14-1.24)</td>
</tr>
</tbody>
</table>

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

\[ HR_{CBC} = \frac{\alpha_1(t)}{\alpha_3(t)} = 0.89 \]

\[ HR_{comp.events} = \frac{\alpha_2(t)}{\alpha_4(t)} = 1.19 \]
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
<table>
<thead>
<tr>
<th>Strengths</th>
<th>Limitations</th>
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<tbody>
<tr>
<td>Nationwide</td>
<td>Over-the-counter drug use</td>
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<tr>
<td>Clinical database – high case validity</td>
<td>Residual confounding</td>
</tr>
<tr>
<td>Use of high quality, demographic and health registries</td>
<td>Compliance to NSAID therapy</td>
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<tr>
<td>Complete follow-up</td>
<td>Rare outcome</td>
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</tbody>
</table>

**Conclusion**

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