Effect of pre-diagnostic NSAID use on ovarian cancer survival

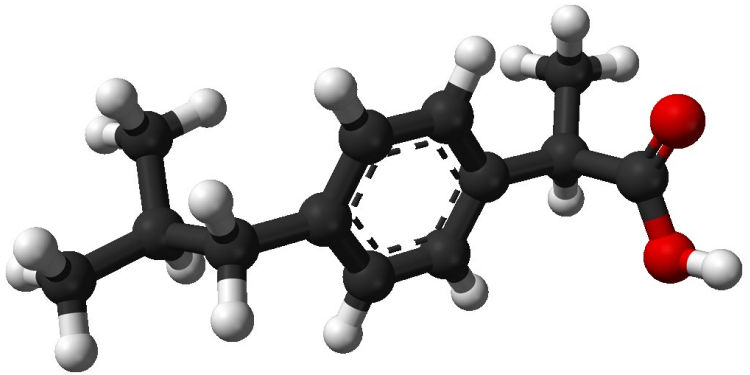
Chris Brown[1], Thomas Ian Barron[2], Kathleen Bennett[2], Linda Sharp[1,3]

1. National Cancer Registry Ireland, 2. Trinity College Dublin, 3. Newcastle University

NSAID indications

National Cancer Registry Ireland

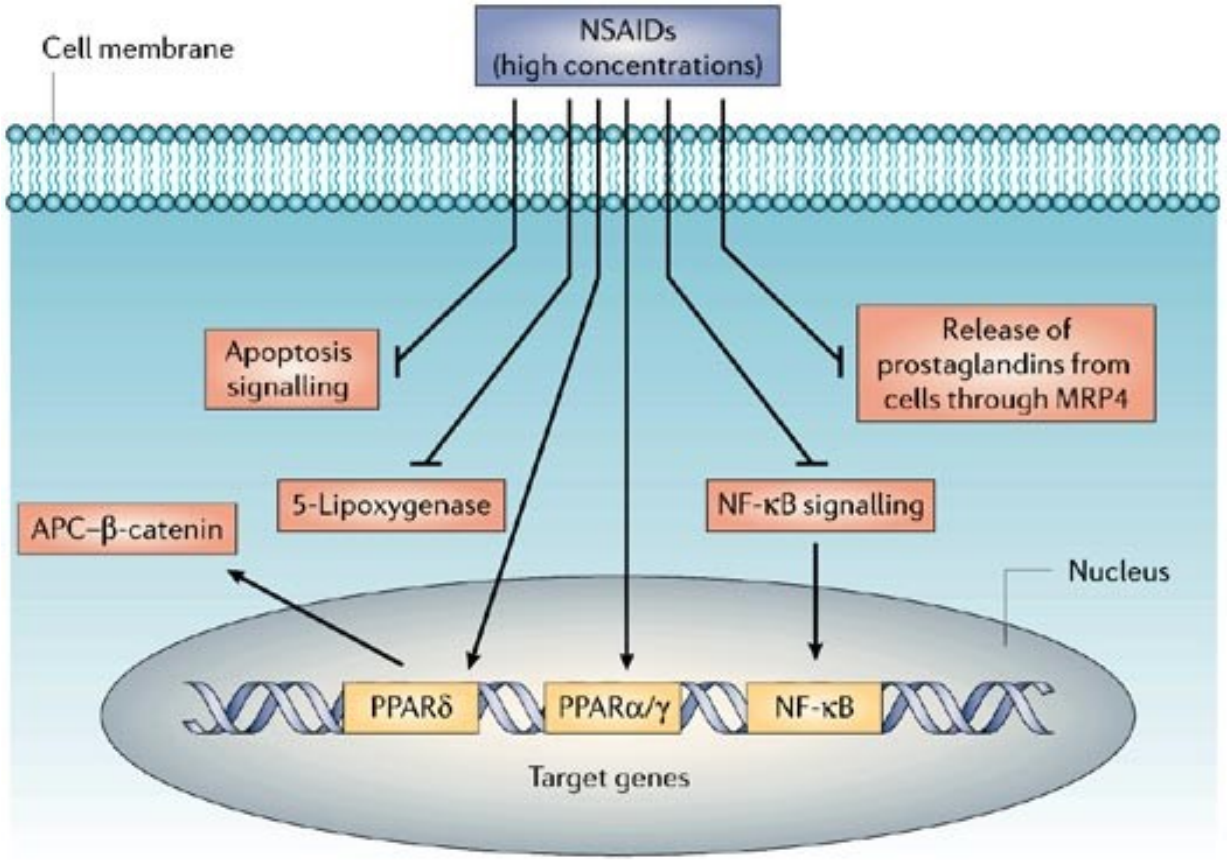
- Mild to moderate pain (analgesic)
  - Migraine
- Inflammation
  - Rheumatoid arthritis
  - Osteoarthritis
- Back pain / soft-tissue disorders
- Ankylosing spondylitis
- Acute gout



doi:10.1038/nrc1801
doi:10.1038/nrc1801

NSAIDs and cancer

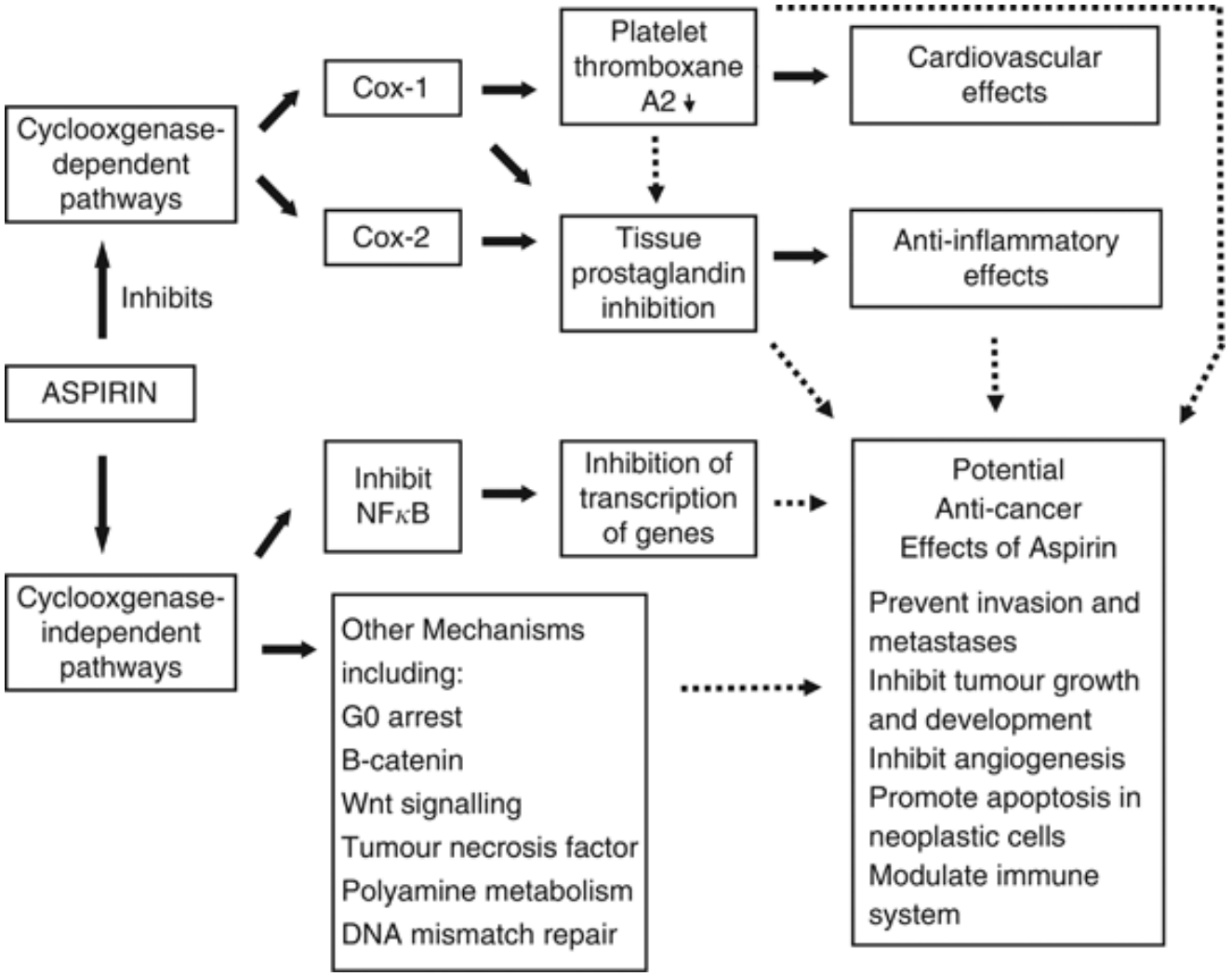
National Cancer Registry Ireland



Cornelia M. Ulrich, Jeannette Bigler & John D. Potter. Non-steroidal anti-inflammatory drugs for cancer prevention: promise, perils and pharmacogenetics. Nature Reviews Cancer 6, 130-140 (February 2006) doi:10.1038/nrc1801

Aspirin and cancer

National Cancer Registry Ireland



R E Langley, S Burdett, J F Tierney, F Cafferty, M K B Parmar and G Venning. *Aspirin and cancer: has aspirin been overlooked as an adjuvant therapy?*. *British Journal of Cancer* (2011) **105**, 1107–1113. doi:10.1038/bjc.2011.289

NSAIDs and cancer

National Cancer Registry Ireland

Short-term effects of daily aspirin on cancer incidence, mortality, and non-vascular death: analysis of the time course of risks and benefits in 51 randomised controlled trials

Peter M Rothwell, Jacqueline F Price, F Gerald R Fowkes, Alberto Zanchetti, Maria Carla Roncaglioni, Gianni Tognoni, Robert Lee, Jill F F Belch, Michelle Wilson, Ziyah Mehta, Tom W Meade

Lancet 2012; 379: 1602–12
Published Online March 21, 2012
DOI:10.1016/S0140-6736(11)61720-0

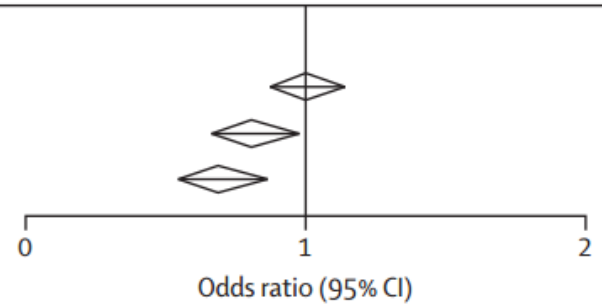
See Comment page 1569
See Articles page 1591
See Articles Lancet Oncol 2012; 13: 518–27

Summary

Background Daily aspirin reduces the long-term risk of death due to cancer. However, the short-term effect is less certain, especially in women, effects on cancer incidence are largely unknown, and the time course of risk and benefit in primary prevention is unclear. We studied cancer deaths in all trials of daily aspirin versus control and the time course of effects of low-dose aspirin on cancer incidence and other outcomes in trials in primary prevention.

Methods We studied individual patient data from randomised trials of daily aspirin versus no aspirin in prevention of vascular events. Death due to cancer, all non-vascular death, vascular death, and all deaths were assessed in all eligible trials. In trials of low-dose aspirin in primary prevention, we also established the time course of effects on incident

	Events/participants		ARR per 1000 patients per year	Odds ratio (95% CI)	$p_{interaction}$
	Aspirin	Control			
Cancers					
0–2·9 years	445/17745	442/17790	−0·06	1·01 (0·88–1·15)	
3·0–4·9 years	193/16463	237/16484	2·19	0·81 (0·67–0·98)	0·04
≥5 years	131/4444	184/4460	4·80	0·70 (0·56–0·88)	



Mario Negri, Milan, Italy (M C Roncaglioni PhD, Prof G Tognoni MD); Institute of Cardiovascular Research, Vascular and Inflammatory

Interpretation Alongside the previously reported reduction by aspirin of the long-term risk of cancer death, the short-term reductions in cancer incidence and mortality and the decrease in risk of major extracranial bleeds with extended use, and their low case-fatality, add to the case for daily aspirin in prevention of cancer.

NSAIDs ovarian cancer risk

National Cancer Registry Ireland

Table 2
Meta-analysis results

	No. of studies	Fixed-effects model RR	(95% CI)
Aspirin			
All studies	9	0.93	(0.81, 1.06)
C-C studies	6	0.85	(0.70, 1.03)
Cohort studies	3	1.00	(0.84, 1.20)
'Regular use'	3	0.89	(0.65, 1.20)
'Irregular use'	3	1.09	(0.87, 1.35)
Duration = 5 years	4	0.73	(0.48, 1.12)
Duration <5 years	4	0.89	(0.69, 1.15)
NA-NSAIDs			
All studies	6	0.88	(0.76, 1.01)
C-C studies	3	0.91	(0.69, 1.22)
Cohort studies	3	0.87	(0.74, 1.01)
'Regular use'	4	0.88	(0.67, 1.15)
'Irregular use'	4	0.92	(0.78, 1.10)
Duration = 5 years	–	–	–
Duration <5 years	–	–	–

RR, Relative risk; CI, confidence interval; NA-NSAIDs, non-aspirin nonsteroidal anti-inflammatory drugs; df, degrees of freedom.

Bonovas S, Filioussi K, Sitaras NM. Do nonsteroidal anti-inflammatory drugs affect the risk of developing ovarian cancer? A meta-analysis. Br J Clin Pharmacol. 2005 Aug;60(2):194–203.

Aspirin survival headlines

National Cancer Registry Ireland

Survival Benefits for Low-Dose **Aspirin** in GI **Cancers**
LWW Journals - 29 Oct 2015
Remarkably, about 75 percent of patients who began a daily **aspirin** regimen after being diagnosed with gastrointestinal **cancers** achieved five-year **survival** ...

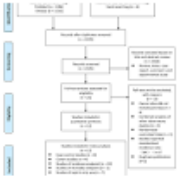
Postdiagnosis **Aspirin** Improves **Survival** in All Gastrointe...
Oncology Nurse Advisor - 14 Oct 2015
The results of the study, involving nearly 14,000 patients, may lead to new insights regarding the use of **aspirin** in GI **cancer**. The study was ...

Cancer Research UK's **aspirin** trial could be a game-chan...
Daily Mail - 22 Oct 2015
The trial is being funded by **Cancer** Research UK and the National Institute ... But the **survival** rate for those not on **aspirin** was just 42 per cent.

Can **aspirin** stop **cancer** returning? World's largest clinical trial begins
Highly Cited - Telegraph.co.uk - 22 Oct 2015

Explore in depth (106 more articles)

Daily **aspirin** may not improve overall prostate **cancer mor**...
2 Minute Medicine (blog) - 2 Nov 2015
1. **Aspirin** use pre- or post-diagnosis of prostate **cancer** was not significant associated with a decrease in prostate-**cancer** specific **survival**. 2.



Aspirin might reduce the incidence of pancreatic **cancer**: A...
Nature.com - 21 Oct 2015
This strategy might obscure true decreases or increases in the incidence or **mortality** risk of pancreatic **cancer** associated with **aspirin**/NSAIDs ...

Too soon for '**aspirin** doubles **cancer survival**' claim
NHS Choices - 28 Sep 2015
"**Aspirin** could almost double your chance of surviving **cancer**," the Daily Mail reports, with most of the newspapers featuring similar claims.

Aspirin 'may double life expectancy of **cancer** patients'
In-Depth - The Guardian - 27 Sep 2015

Explore in depth (137 more articles)

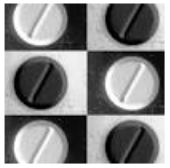
Prostate **cancer**: Scientists develop early blood test to see ...
The Independent - 4 Nov 2015
... test to see whether men with advanced prostate **cancer** can benefit from a new drug that can significantly improve their chances of **survival**.

Aspirin may double **survival** for **cancer** patients
Medical News Today - 29 Sep 2015
Aspirin may double the chances of **survival** for patients with gastrointestinal **cancers**, according to the results of a new study recently presented ...

Aspirin can protect against **cancer** - and treat it, according to new ...
In-Depth - The Independent - 1 Oct 2015

Explore in depth (84 more articles)

Aspirin: is it really a 'wonder drug'?
Medical News Today - 29 Oct 2015
Cancer is just one in a long line of illnesses that **aspirin** may combat. ... a health care provider - for heart attack **survivors** and others at high risk ...



Aspirin appears to extend **survival** with most gastrointesti...
The Australian Financial Review - 5 Oct 2015
As a follow-up, the effect of a daily low dose **aspirin** on the **survival** of elderly patients with bowel **cancer** is under way in the Netherlands.

https://www.google.ie/search?q=aspirin%20cancer%20survival&tbm=nws

AOCS case-control study

National Cancer Registry Ireland

Contents lists available at ScienceDirect

Cancer Epidemiology

The International Journal of Cancer Epidemiology, Detection, and Prevention

journal homepage: www.canceepidemiology.net

Short communication

Aspirin, nonaspirin nonsteroidal anti-inflammatory drugs, acetaminophen and ovarian cancer survival

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ABSTRACT

Aspirin and nonaspirin nonsteroidal anti-inflammatory drugs (NSAIDs) have been shown to decrease tumor progression in pre-clinical models of ovarian cancer, however the influence of these drugs on survival in women following a diagnosis of ovarian cancer is unknown. We included 1305 Australian women diagnosed with incident invasive epithelial ovarian cancer, recruited into a population-based case–control study. Use of aspirin, nonaspirin NSAIDs and acetaminophen in the 5 years preceding ovarian cancer diagnosis was assessed from self-reports. Deaths were ascertained up to October 2011 via linkage with the Australian National Death Index. Cox proportional hazards regression models were used to calculate adjusted hazard ratios (HRs) and 95% confidence intervals (CI). During a mean follow-

Our results provide no strong evidence that pre-diagnostic use of aspirin or nonaspirin NSAIDs are associated with improved survival in women with ovarian cancer.

mortality. Associations did not differ by histologic subtype, age at diagnosis or stage. Given current interest in the role of aspirin and nonaspirin NSAIDs in cancer survival these results are noteworthy given they are the first to investigate these associations in women with ovarian cancer. Our results provide no strong evidence that pre-diagnostic use of aspirin or nonaspirin NSAIDs are associated with improved survival in women with ovarian cancer.

HOPE case-control study

National Cancer Registry Ireland

Published OnlineFirst June 10, 2015; DOI: 10.1158/1055-9965.EPI-15-0508

Null Results in Brief

Cancer Epidemiology, Biomarkers & Prevention

Use of Common Analgesics Is Not Associated with Ovarian Cancer Survival

Albina N. Minlikeeva[1], Jo L. Freudenheim[1], Wei-Hsuan Lo-Ciganic[2], Kevin H. Eng[3], Grace Friel[4], Brenda Diergaarde[5], Francesmary Modugno[6], Rikki Cannioto[4], Emily Gower[4], J. Brian Szender[7], Kassondra Grzankowski[7], Kunle Odunsi[7], Roberta B. Ness[8], and Kirsten B. Moysich[1,4,9]

Pre-diagnostic intake of analgesics may not be Associated with ovarian cancer outcomes.

Abstract

Background: Use of analgesics has been associated with lower risk of ovarian cancer, but, to date, very few studies have explored the association between analgesics and ovarian cancer survival.

Methods: We examined the relationship between self-reported prediagnostic use of aspirin, ibuprofen, and acetaminophen and overall survival (OS), progression-free survival (PFS), ascites at the time of primary treatment, and persistence of disease after primary treatment among 699 women diagnosed with epithelial ovarian carcinoma. The associations between use of these medications and OS and PFS were estimated using Cox proportional hazards models. We utilized unconditional logistic regression models to estimate associations between medication use and presence of ascites and persistence of disease.

Results: Prediagnostic intake of aspirin, both low-dose and regular-dose, ibuprofen, and acetaminophen was not associated with any of the outcomes of interest.

Conclusions: Our results indicate a lack of association between prediagnostic intake of selected analgesics and OS, PFS, presence of ascites at the time of primary treatment, and persistence of disease after primary treatment.

Impact: Prediagnostic intake of analgesics may not be associated with ovarian cancer outcomes. *Cancer Epidemiol Biomarkers Prev; 24(8); 1291–4. ©2015 AACR.*

Iwoa women's health study

National Cancer Registry Ireland

OXFORD JOURNALS CONTACT US MY BASKET MY ACCOUNT

JNCI Journal of the National Cancer Institute

ABOUT THIS JOURNAL CONTACT THIS JOURNAL SUBSCRIPTIONS CURRENT ISSUE ARCHIVE SEARCH

Oxford Journals › Medicine & Health › JNCI J Natl Cancer Inst › Volume 99, Issue 11 › Pp. 881-889.

Association of Aspirin and Nonaspirin Nonsteroidal Anti-inflammatory Drugs With Cancer Incidence and Mortality

Aditya Bardia, Jon O. Ebbert, Robert A. Vierkant, Paul J. Limburg, Kristin Anderson, Alice H. Wang, Janet E. Olson, Celine M. Vachon and James R. Cerhan

+ Author Affiliations

Correspondence to:
Jon O. Ebbert, MD, Department of Internal Medicine, Mayo Clinic College of Medicine, 200 First St SW, Rochester, MN 55905 (e-mail: ebbert.jon@mayo.edu).

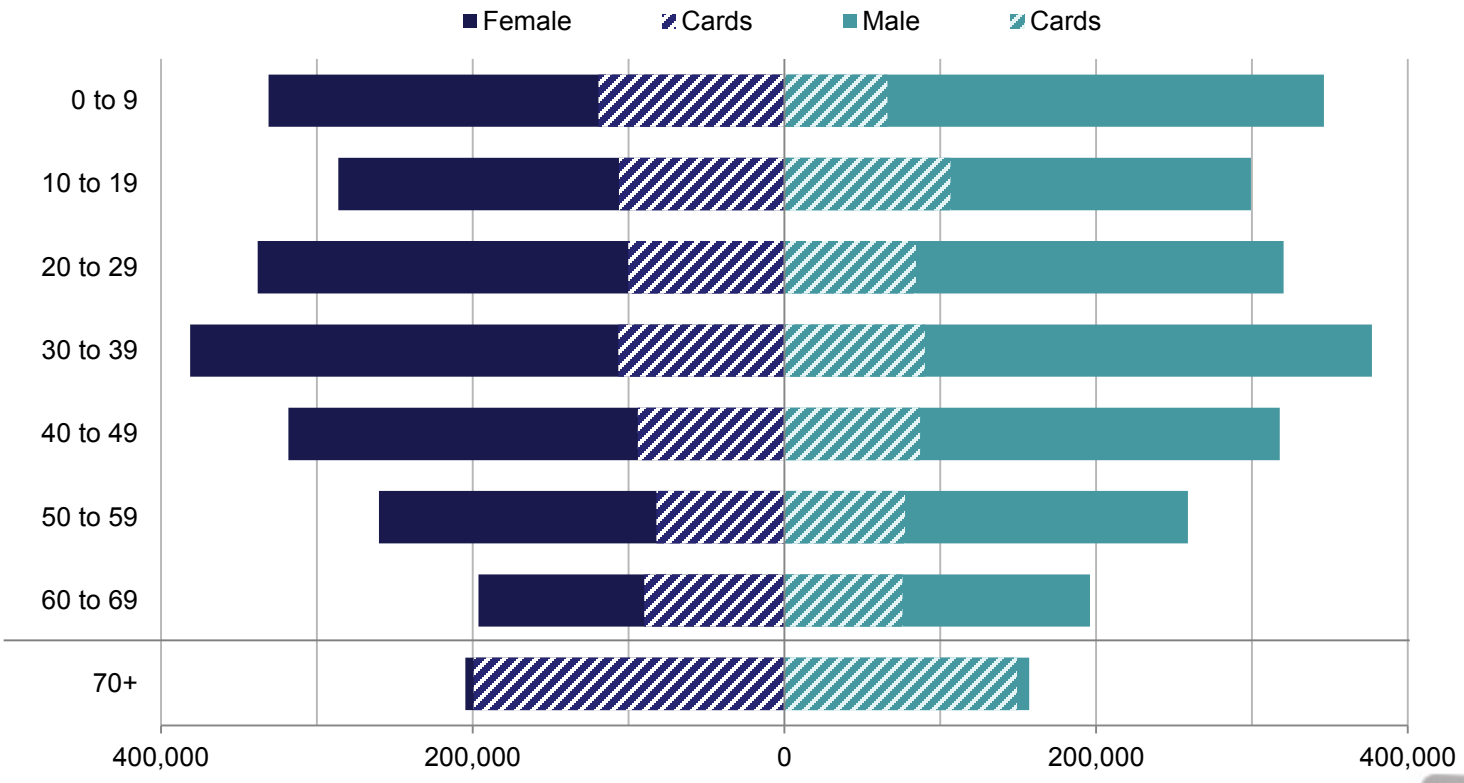
Received November 28, 2006.
Revision received March 2, 2007.
Accepted April 20, 2007.

Aspirin or NSAID use, times per week	Cancer mortality: No. of events	Cancer mortality: Adjusted RR (95% CI)
Aspirin use		
Never	366	1.00 (referent)
Ever	827	0.87 (0.76 to 0.99)
≤1	419	0.91 (0.78 to 1.06)
2–5	196	0.83 (0.69 to 1.00)
≥6	212	0.82 (0.68 to 0.99)
P_{trend}		.02
NSAID use		
Never	717	1.00 (referent)
Ever	476	1.05 (0.92 to 1.12)
≤1	218	1.01 (0.86 to 1.20)
2–5	95	1.04 (0.82 to 1.31)
≥6	163	1.13 (0.92 to 1.37)
P_{trend}		.28
Combined use		
Never	216	1.00 (referent)
Aspirin only	501	0.89 (0.75 to 1.06)
NSAID only	150	1.10 (0.88 to 1.39)
Both	326	0.92 (0.76 to 1.10)

Irish pharmacy data

National Cancer Registry Ireland

Irish population (and medical cards) in 2011

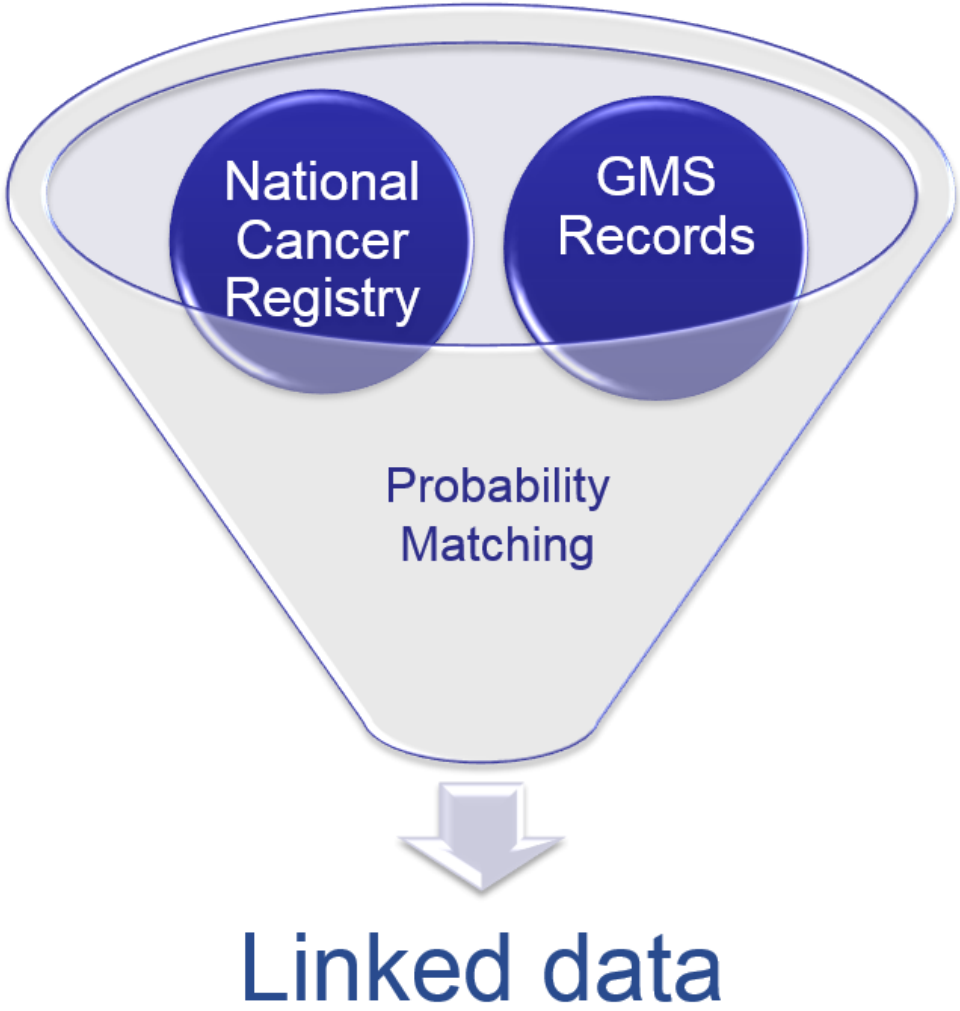


http://www.cso.ie/en/media/csoie/census/documents/census2011pdr/Census,2011,Highlights,Part,1,web,72dpi.pdf

Prescription data linkage

National Cancer Registry Ireland

All women diagnosed with invasive ovarian cancer (ICD10-C56) between 2001-2011 were linked to GMS card records



Methods

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- Associations between any pre-diagnosis NSAID exposure and cause-specific survival using Cox regression
  - Models adjusted for: age, smoking, marital status, diagnosis year, urban/rural residence, deprivation, stage, grade, and surgery at diagnosis.
  - Alive cases censored on 31/12/2012
- Secondary: Adjusting for competing risks

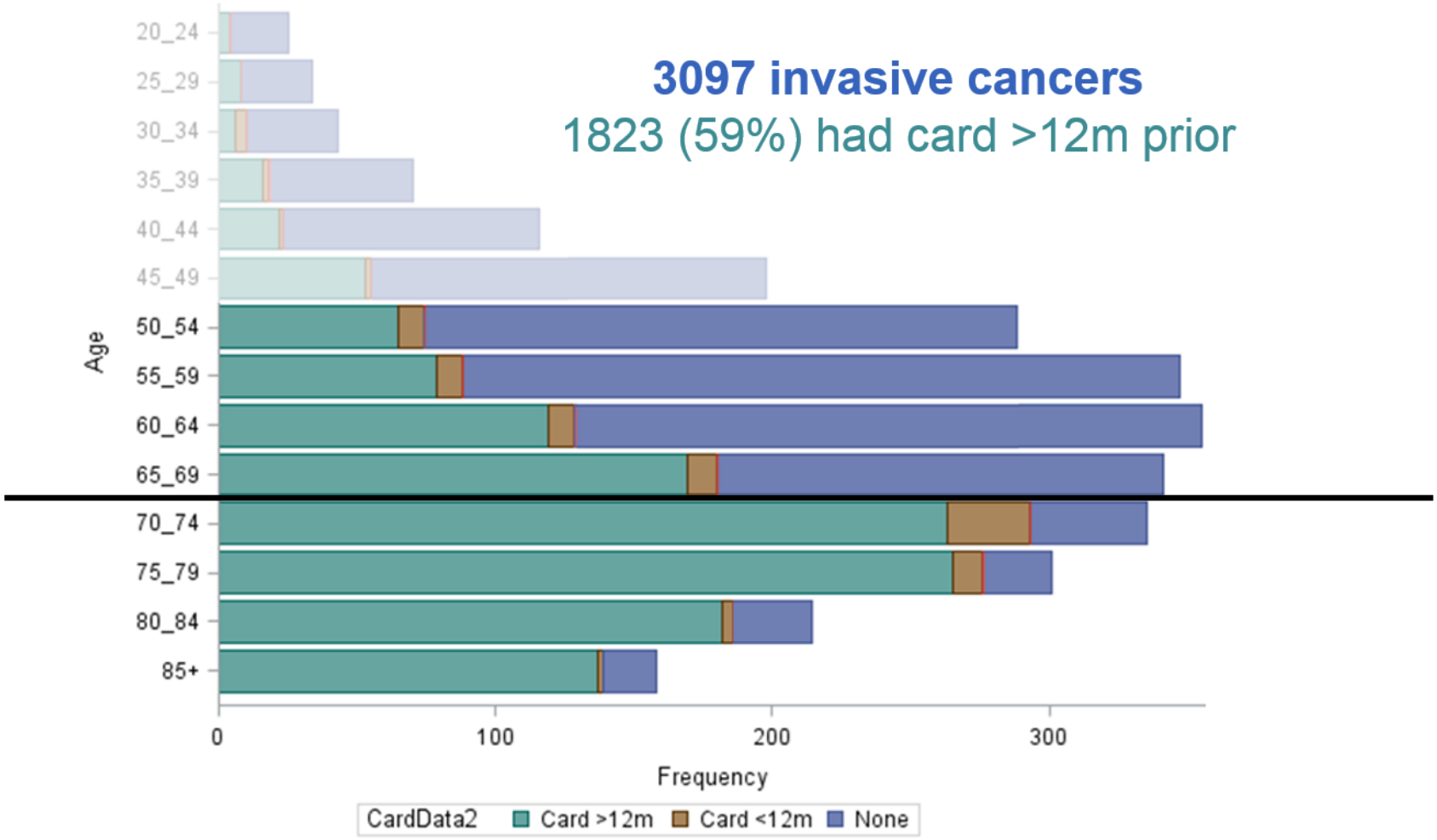
- Pre-planned subgroup analysis
  - Aspirin, Other NSAID, Both

Published protocol

ENEPD European Network of Centres for Pharmacoepidemiology and Pharmacovigilance

Ovarian cancers 2001-2010

National Cancer Registry Ireland

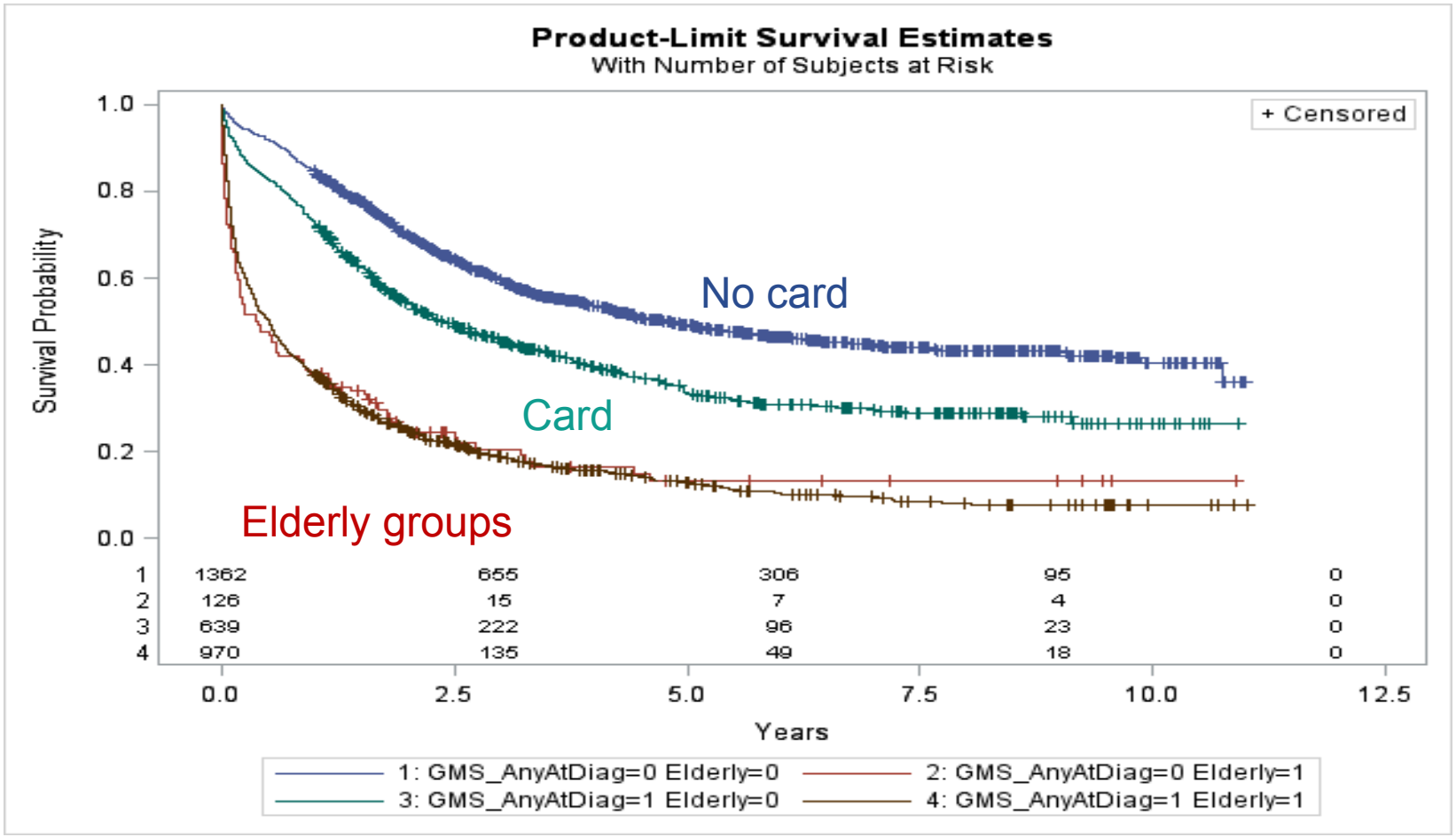


Brown C, Barron TI, Bennett K, MacDonald D, Dwane F, Sharp L. Generalisability of pharmacoepidemiological studies using restricted prescription data. Ir J Med Sci. 2015 Oct 6;1–5.

This is a selected cohort

National Cancer Registry Ireland

More smokers, Older, deprived, employed less….



Over the counter drugs?

National Cancer Registry Ireland

In many countries these medications could be purchased over the counter…

In our medical-card population, those taking *these* drugs would likely have a prescription

Exposure pre-diagnosis

National Cancer Registry Ireland

Characteristic		N	NSAID (%)
Age at diagnosis	<60	325	172 (52.9)
	60-69	373	220 (59.0)
	70-79	679	444 (65.4)
	80-89	392	254 (64.8)
	90+	54	33 (61.1)
Deprivation quintile	1 – Least dep.	236	142 (60.2)
	2	200	115 (57.5)
	3	260	164 (63.1)
	4	306	184 (60.1)
	5 – Most dep.	703	445 (63.3)
Marital status	Married	722	444 (61.5)
	Single	319	187 (58.6)
	Other	782	492 (62.9)
Population density	High-urban	639	405 (63.4)
	Intermed.-urban	368	239 (64.9)
	Rural	678	391 (57.7)

Characteristic		N	NSAID (%)
Smoking status	Current	277	167 (60.3)
	Never smoked	880	528 (60.0)
	Unknown	499	318 (63.7)
Grade	Well	84	52 (61.9)
	Moderately	203	124 (61.1)
	Poorly	568	342 (60.2)
	Undifferentiated	24	17 (70.8)
	Missing	944	588 (62.3)
Tumour stage	1	257	167 (65.0)
	2	148	88 (59.5)
	3	535	325 (60.7)
	4	577	360 (62.4)
	Missing	306	183 (59.8)

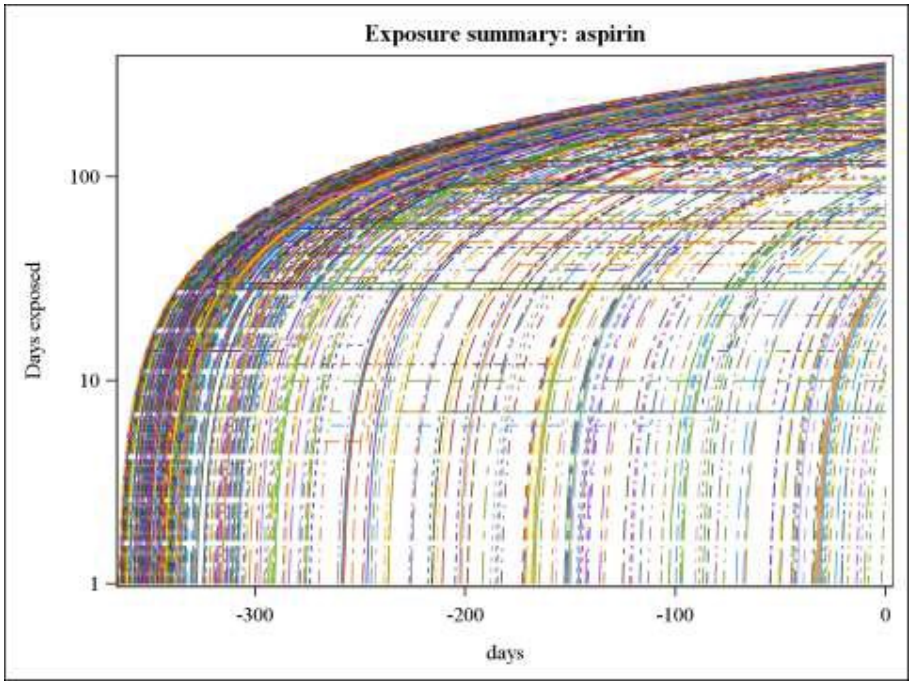
Drug Class		N	%
Class	**None**	**700**	**38%**
	Aspirin	**311**	**17%**
	Other NSAIDs	**538**	**30%**
	Both	**274**	**15%**

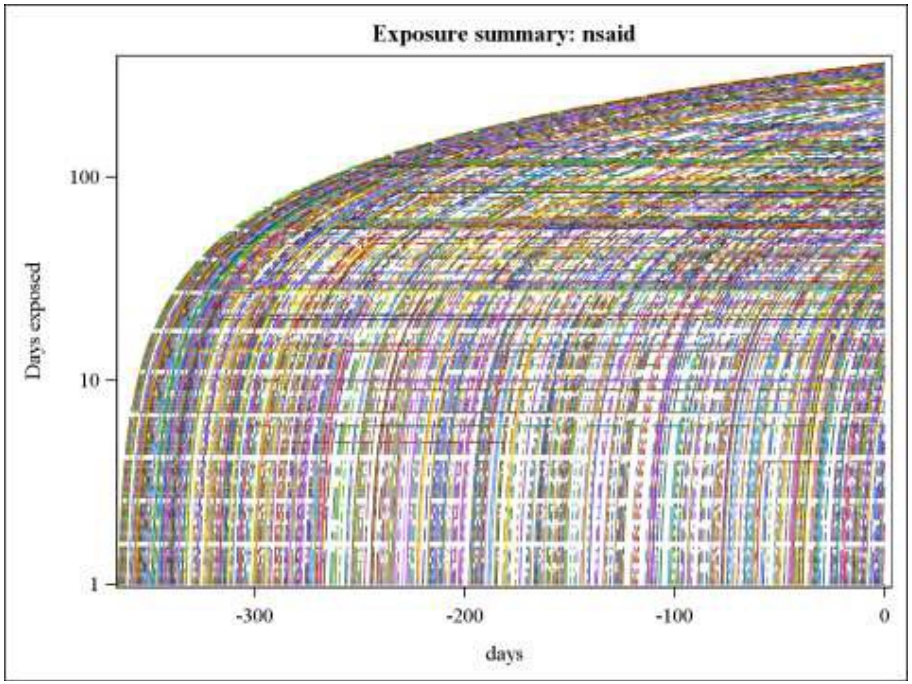
Exposure pre-diagnosis

National Cancer Registry Ireland

Aspirin users are consistent users

Other NSAIDs are used less consistently

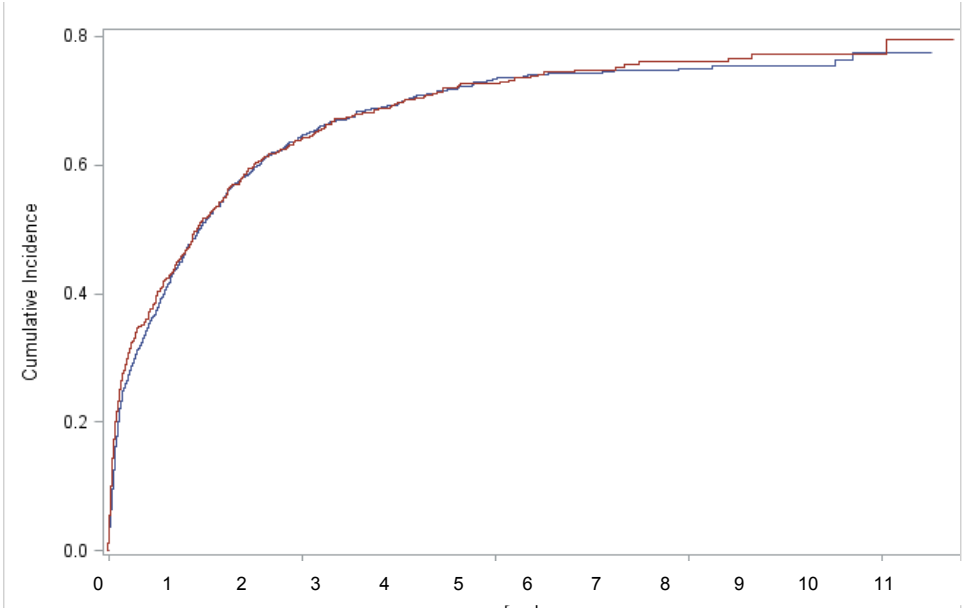




Cumulative incidence of death

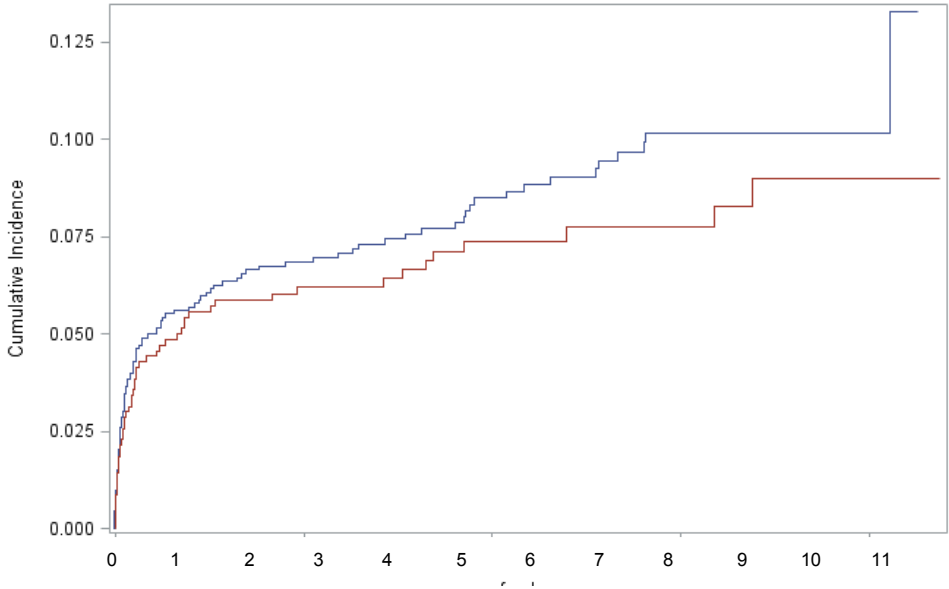
National Cancer Registry Ireland

Ovarian cancer



Years from diagnosis

Other causes



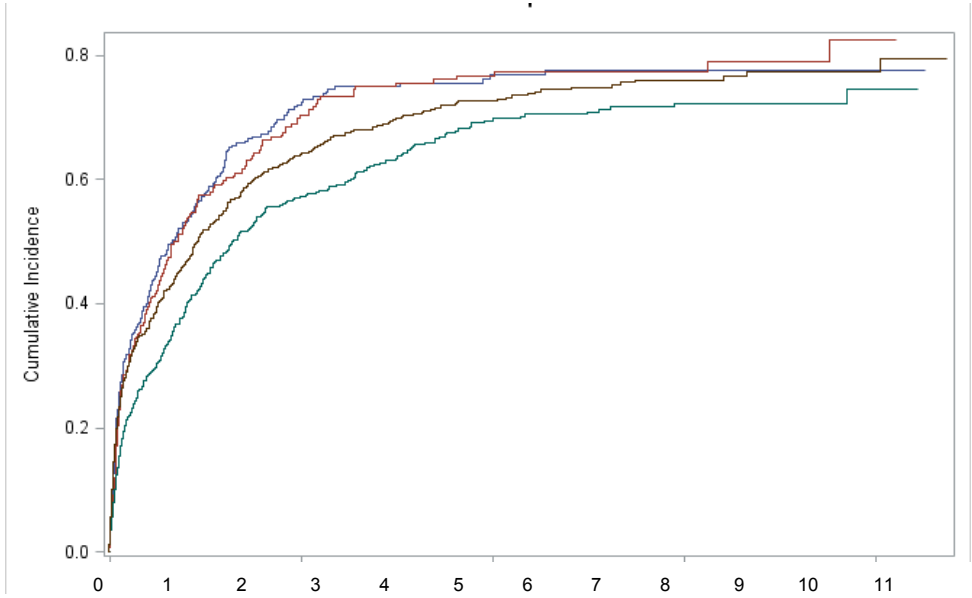
Years from diagnosis

Any NSAID — None

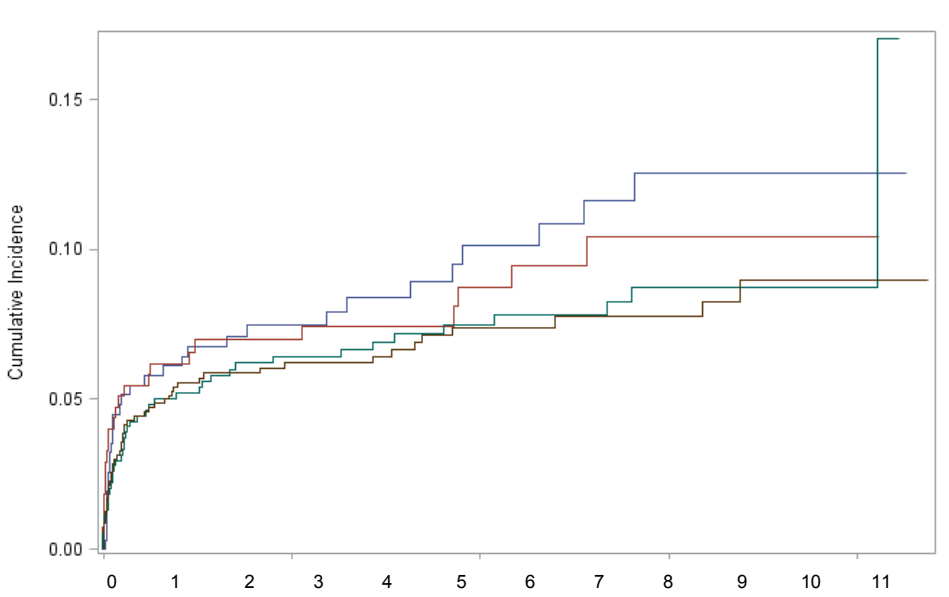
Effect by drug class

National Cancer Registry Ireland

Ovarian cancer



Other causes



Aspirin (n=538)

Both (n=274)

Other NSAIDs (n=538)

None (n=700)

Summary results

National Cancer Registry Ireland

Overall adjusted effects…

Model*		Ovarian cancer death HR (95%CI)	Other death HR (95%CI)
Pre-diagnostic	Cause-specific	0.84 (0.74, 0.96)	0.62 (0.42, 0.93)
	Competing-risks	0.90 (0.78, 1.05)	0.75 (0.50, 1.11)

**Models adjusted for* age, smoking, marital status, diagnosis year, urban/rural residence, deprivation, stage, grade, and surgery at diagnosis

Effects by drug class

National Cancer Registry Ireland

Adjusted effects…

Model*		Ovarian cancer death HR (95%CI)	Other death HR (95%CI)
Test of interaction		P=0.14	P=0.065
Pre-diagnostic	Aspirin	0.89 (0.74, 1.06)	0.69 (0.41, 1.16)
	Other NSAIDs	0.83 (0.71, 0.97)	0.62 (0.38, 0.99)
	Both	0.81 (0.67, 0.98)	0.54 (0.30, 0.98)

**Models adjusted for* age, smoking, marital status, diagnosis year, urban/rural residence, deprivation, stage, grade, and surgery at diagnosis

Conclusion

National Cancer Registry Ireland

This is one of the largest observational studies of NSAID use in ovarian cancer:

- Some association between pre-diagnostic exposure and cancer-specific survival.
- Unconfirmed if drug class is relevant.

This analysis is being replicated in Northern Ireland (NICR) and English (CPRD) populations.

N. Ireland Cancer Registry

Queen's University Belfast

CPRD MORE DIMENSIONS TO DATA

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- Staff at National Cancer Registry of Ireland, in particular:
  - **The data team** for linkage of GMS records,
  - **Tumour registration officers** for collecting data
- **HSE-PCRS** for providing the GMS prescription data
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