

NSAID Use Is Associated with Lower Mammographic Breast Density in Younger Women

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ABSTRACT

Background: Use of aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs) has been associated with a decrease in breast cancer risk. It is unknown whether NSAIDs are also associated with lower mammographic breast density, a strong intermediate marker of breast cancer risk. Such information would help determine underlying pathways linking NSAIDs and breast cancer.
Objectives: We undertook a study investigating NSAID use and mammographic breast density in 29,284 postmenopausal women who had at least two screening mammograms after 1996 at Group Health Cooperative based in Seattle, Washington, in the United States (average time between exams = 1.7 years).
Methods: We used automated pharmacy records to identify use of these NSAIDs: aspirin propionic acid, indole/indene acid, anthranilic acid, enolic acid, heteroaryl acetic acid, alkanes, and COX-2 inhibitors. We classified women as NSAID non-users, continuers, initiators, or discontinuers based on use between the 2 mammograms. Density was classified by the Breast Imaging Reporting and Data System. We used unordered polytomous logistic regression methods to model the odds of staying not dense, decreasing, or increasing density relative to remaining dense, adjusting for hormone therapy use, obesity, and time between exams.
Results: There was no association between NSAID use and mammographic breast density among women 65 and older. Among women less than 65 years of age, women who used NSAIDs were more likely to have their mammographic breast density stay not dense (odds ratio (OR)=1.2, 95% confidence interval (CI)=1.1-1.3), or to decrease (OR=1.1, 95% CI=1.0-1.2) relative to women whose mammographic breast density remained dense between the two mammograms. NSAID discontinuation was not associated with an increase in mammographic breast density.
Conclusions: The NSAID-mammographic breast density association was stronger for NSAIDs continuers between the 2 time points than for initiators, suggesting either long term use may be needed to lower mammographic density or other lifestyle factors associated with NSAID use may explain the relation between NSAID use and breast cancer risk.

PURPOSE

- Examine whether aspirin & non-steroidal anti-inflammatories drugs (NSAIDs) are associated with * mammographic density
- Investigate whether initiation of aspirin & other NSAIDS leads to a decrease in mammographic breast density

BACKGROUND

- Many epidemiologic studies have observed inverse associations between aspirin and NSAID use & breast cancer risk
- NSAIDs inhibit Cyclooxygenase (COX)
 - COX catalyzes the synthesis of prostaglandins
 - PGE₂ * *aromatase* gene expression & may play a role in non-estrogen dependent pathways
- Mammographic breast density is one of the strongest breast cancer risk factors (4-6 fold)
- Unknown whether aspirin &/or NSAID use is associated with * mammographic density

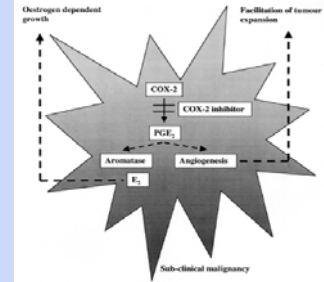


Figure: Possible effects of cyclooxygenase-2 (COX-2) inhibitors as breast cancer chemopreventives. PGE₂, prostaglandin E₂. Source: Davies *et al Annals of Oncology* 2002

METHODS

- 29,284 women enrolled in Group Health's breast cancer screening program (Integrated Group Practice based in WA, USA)
- 2+ mammograms per person (average time between the two mammograms = 1.7 years)
- Exposure:
 - Automated pharmacy dispensing records
 - Aspirin and NSAID use classified into the following 9 categories: Aspirin, propionic acid, indole/indene acids, anthranilic acids, enolic acids, heteroaryl acetic acid, alkanes, and COX-2 inhibitors
 - Examined by class & by non-prescription, prescription, and any NSAID
 - Initiators, Continuers, Discontinuers, and Non-users are based on use by category between the two exams
- Outcome based on 4-category BI-RADS density ratings at each exam: almost entirely fat, scattered fibroglandular tissue, heterogeneously dense & extremely dense
 - Stays dense, increased density, decreases density and stays not dense
- Population: ~90% aged 50-79 years; 89% white, 7% African American, 4% other; ~1/3 women obese (>30 kg/m²)

STATISTICAL ANALYSES

- Unordered polytomous regression
- Adjusted for age, hormone replacement therapy (HRT) use at each exam, body mass index (BMI) at 1st exam, & time between exams

RESULTS

Distribution of Mammographic Breast Density at Both Exams

1st Mammogram	N	Breast density at 2nd Mammogram			
		Almost entirely Fat Row %	Fibroglandular Row %	Heterogeneous Row %	Extremely Dense Row %
Non-user					
Almost entirely Fat	1914	45.4	50.8	3.5	0.3
Fibroglandular	9046	7.5	67.2	24.7	0.6
Heterogeneous	8170	0.4	22	70	7.5
Extremely Dense	1523	0.1	3	49.1	47.9
Initiator					
Almost entirely Fat	736	47.7	48.9	3.3	0.1
Fibroglandular	3159	8.6	67.9	23	0.5
Heterogeneous	2326	0.6	24.9	67.8	6.7
Extremely Dense	373	0	0.8	53.6	45.6
Discontinuer					
Almost entirely Fat	151	48.3	49.7	2	0
Fibroglandular	785	7.6	69.2	22.6	0.6
Heterogeneous	608	0.2	28	66.9	4.9
Extremely Dense	92	0	2.2	54.4	43.5
Continuer					
Almost entirely Fat	146	49.3	49.3	1.4	0
Fibroglandular	547	9.3	68	22.7	0
Heterogeneous	315	0.3	24.6	79.4	5.6
Extremely Dense	45	0	2.2	48.9	48.9

Multivariable odds* of breast density increasing, decreasing, or staying the same between mammograms stratified by age & NSAID initiators and continuers – all relative to non-users

	Initiator v. Non-users Analysis		Continuers v. Non-users Analysis	
	<65 Years OR (95% CI)	65+ Years OR (95% CI)	<65 Years OR (95% CI)	65+ Years OR (95% CI)
Non-Prescription NSAIDs				
Stays dense	1	1	1	1
Increase	1.1 (0.9-1.2)	1.0 (0.9-1.2)	1.0 (0.7-1.6)	1.1 (0.8-1.6)
Decrease	1.1 (0.9-1.3)	1.0 (0.9-1.2)	1.1 (0.7-1.7)	1.0 (0.7-1.5)
Stays Not Dense	1.2 (1.1-1.3)	1.0 (0.9-1.1)	1.4 (1.0-1.8)	1.2 (0.9-1.5)
Prescription NSAIDs				
Stays dense	1	1	1	1
Increase	1.0 (0.8-1.3)	0.9 (0.7-1.2)	1.3 (0.8-2.2)	0.8 (0.5-1.4)
Decrease	1.1 (0.9-1.4)	0.8 (0.6-1.1)	0.9 (0.5-1.7)	0.7 (0.4-1.3)
Stays Not Dense	1.1 (1.0-1.3)	1.0 (0.8-1.2)	1.1 (0.8-1.7)	0.8 (0.6-1.2)
Any NSAID				
Stays dense	1	1	1	1
Increase	1.0 (0.9-1.2)	1.0 (0.9-1.2)	1.1 (0.8-1.6)	1.1 (0.8-1.4)
Decrease	1.1 (0.9-1.2)	1.0 (0.8-1.2)	1.0 (0.7-1.5)	0.9 (0.6-1.3)
Stays Not Dense	1.2 (1.1-1.3)	1.0 (0.9-1.1)	1.3 (1.0-1.6)	1.1 (0.9-1.4)

*Adjusted for: hormone replacement therapy (HRT) use at each exam, body mass index (BMI) at 1st exam, & time between exams & age within strata

STRENGTHS & LIMITATIONS

- Large prospective study without recall bias
- Duration between mammograms & drug use may not have been long enough to observe an effect
- Lack data on other possible confounders and indications for use

CONCLUSIONS

- No strong association between NSAIDs and breast density
- Women <65
 - NSAID use associated with staying non-dense (vs. staying dense)
 - Associations were modest & slightly stronger for continuers than initiators
- Unmeasured confounders may differ between continuers and initiators
- Long-term NSAID use may be needed to * density
- Women 65+ years
 - NSAID use is unlikely to lead to decrease mammographic breast density