Non-Steroidal Anti-Inflammatory Drugs and Prostate Cancer Risk in the VITamins And Lifestyle (VITAL) Cohort

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Abstract

Introduction: Chronic inflammation may be important in prostate carcinogenesis. Several epidemiologic studies have reported inverse associations between non-steroidal anti-inflammatory drugs (NSAIDs) and prostate cancer risk, although many studies are limited by assessment of short-term use only.

Methods: Participants were male members of the VITamins And Lifestyle cohort, comprised of 34,132 men, age 50-76 years, living in western Washington State. Cox proportional hazards models were used to estimate adjusted hazard ratios (HR) and 95% confidence intervals (95% CI) of 10-year average use of individual NSAIDs with total prostate cancer (n=1,550) and prostate cancer by grade.

Results: Low-dose aspirin, regular-strength aspirin, ibuprofen, and any non-aspirin NSAID (ibuprofen, naproxen, and COX-2 inhibitors) were not associated with prostate cancer risk. There was a suggestion that regular-strength aspirin was inversely associated with risk of high-grade cancer (HR 0.73, 95% CI: 0.53-1.02).

Conclusion: NSAID use was not associated with prostate cancer risk in the VITAL cohort.

Impact: Our findings do not support the use of NSAIDs for chemoprevention of prostate cancer.
**Introduction**

There is increasing evidence which suggests that chronic inflammation is important in prostate carcinogenesis (1, 2). Prostatitis has been associated with prostate cancer risk and proliferative inflammatory atrophy of the prostate, a condition marked by chronic inflammation, may be an early precursor lesion for prostate cancer (1, 2). Non-steroidal anti-inflammatory drugs (NSAIDs) have anti-cancer properties *in vitro* and *in vivo* (3, 4), in support of epidemiologic studies which have shown reductions in prostate cancer risk for aspirin use in particular (5). Many epidemiologic studies of NSAID use and prostate cancer risk, however, are limited by short-term measurement of NSAID use and most do not adjust for indications of use.

Here we examine the association of long-term NSAID use with prostate cancer risk in the VITamins And Lifestyle (VITAL) cohort study.

**Methods**

*Study Population*

Participants were male members of the VITAL cohort (6). Men, age 50-76 years, living in the region of Washington State covered by the Surveillance, Epidemiology, and End Results (SEER) cancer registry, were eligible to participate. Between October 2000 and November 2002, we mailed baseline questionnaires to 195,465 men. Of these, 37,382 (19.1%) were returned and deemed eligible for inclusion in the VITAL cohort. For this analysis, exclusions were made for men who: had a history of prostate cancer (n=2,013), were missing key variables (cancer history at baseline or NSAID use [n=1,235]), or had a subsequent diagnosis of incident *in situ* prostate cancer (n=2), leaving, 34,132 available for analysis.
Data Collection

Participants completed a baseline questionnaire which included questions on regular use (≥1 day/week for ≥1 year) of NSAIDs, including frequency and years of use in the past 10 of low-dose aspirin, regular or extra-strength aspirin, ibuprofen, naproxen, and celecoxib/rofecoxib. Ten-year average use of each drug was categorized into non-user; low use, <4 days/week or <4 years; and high use, ≥4 days/week and ≥4 years. Participants also reported on known or suspected risk factors for prostate cancer as well as health conditions that are possible indications of NSAID use.

Case Ascertainment

Participants were followed for incident prostate cancer diagnoses via linkage to the SEER registry. Between baseline and December 31, 2007, there were 1,550 incident prostate cancer cases diagnosed. High-grade tumors were defined as Gleason scores 8-10 and 7 (4+3). Low-grade tumors were Gleason scores 2-6 or 7 (3+4). As primary and secondary Gleason scores were not available from SEER for prostate cancers diagnosed prior to 2004, analyses by grade were restricted to incidence data from 2004-2007 only (733 low-grade and 213 high-grade).

Statistical Analysis

We estimated hazard ratios (HR) and 95% confidence intervals (95% CI) for total prostate cancer and prostate cancer by grade in relation to NSAID use with Cox proportional hazards regression models, using participants’ age as the time metric. Prostate cancer risk factors as well as potential indications for NSAID use were identified a priori for adjustment in multivariable models (see footnote b of Table 1). P-values for trend were calculated by treating categorical variables as ordinal in the models. We calculated minimum detectable risks (MDR) given 80% power (7). For comparisons of use to non-use of each NSAID, we had an MDR of

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Results

Use of NSAIDs was not associated with total prostate cancer risk (Table 1). When the analysis was stratified by prostate cancer grade (Table 2), use of regular-strength aspirin was suggestive of an inverse association with high- (HR 0.73, 95% CI: 0.53-1.02) but not low-grade (HR 1.04, 95% CI: 0.89-1.23) prostate cancer. No differences were observed for the remaining NSAIDs by grade or by stage (local vs. regional/distant; data not shown).

Discussion

We observed no association of use of individual NSAIDs with total prostate cancer risk in this cohort. In contrast to our findings, two recent meta-analyses reported 11% (HR 0.89, 95% CI: 0.77-1.03) (8) and 17% (HR 0.83, 95% CI: 0.76-0.91) (5) reductions in total prostate cancer risk among six and nine prospective studies of aspirin use, respectively. It may be that the null result we observed with aspirin use and total prostate cancer risk is due to residual confounding by PSA testing, as we only collected data on PSA testing at baseline. If aspirin use is positively associated with subsequent prostate cancer screening, a small reduction in risk would be negatively confounded towards 1.0.

One meta-analysis reported on the association of NSAID use with advanced prostate cancer; in it aspirin use was associated with a 17% (HR 0.83, 95% CI: 0.73-0.95) reduction in risk among six prospective studies (5). Our finding of a 27% statistically non-significant lower risk of high-grade prostate cancer among users of regular-strength aspirin is consistent with this estimate (5). In support of our findings, the meta-analyses did not find a reduction in risk of total (5, 8) or advanced (5) prostate cancer among prospective studies of non-aspirin NSAIDs.
The advantages of this study include its assessment of NSAID use over a 10-year period prior to baseline, and the separate assessment of use of low-dose aspirin, regular dose aspirin, ibuprofen, naproxen, and COX-2 inhibitors. We were also able to control for confounding by multiple indications for NSAID use. Nonetheless, these differences do not explain the discrepancies between our findings and those of other published reports.

In summary, our findings do not support an association of NSAID use with prostate cancer risk, but do provide limited support for a reduction in high-grade prostate cancer with aspirin use.
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Table 1. Associations between NSAIDs and total prostate cancer risk among male VITAL participants, 2000-2007 (n=34,132).

| NSAID                | Cases n = 1,550 N (%) | Non-Cases n = 32,582 N (%) | Age-Adjusted HR (95% CI)\(^a\) | Multivariable-Adjusted HR (95% CI)\(^a,b\) |
|----------------------|-----------------------|----------------------------|---------------------------------|----------------------------------------|
| **Low-Dose Aspirin** |                       |                            |                                 |                                        |
| Non-User             | 965 (62.83)           | 21,552 (66.73)             | 1.00 referent                   | 1.00 referent                          |
| User                 | 571 (37.17)           | 10,746 (33.27)             | 1.04 (0.94-1.16)                | 1.03 (0.92-1.15)                       |
| 10-year average use\(^c\) |                     |                            |                                 |                                        |
| Non-User             | 965 (65.92)           | 21,552 (69.94)             | 1.00 referent                   | 1.00 referent                          |
| Low                  | 252 (17.21)           | 4,831 (15.68)              | 1.09 (0.95-1.25)                | 1.07 (0.93-1.24)                       |
| High                 | 247 (16.87)           | 4,430 (14.38)              | 1.03 (0.89-1.18)                | 1.02 (0.88-1.19)                       |
| p-trend              |                       |                            | 0.49                            | 0.57                                   |
| **Regular-Strength Aspirin** |                |                              |                                 |                                        |
| Non-User             | 1,037 (67.03)         | 22,228 (68.43)             | 1.00 referent                   | 1.00 referent                          |
| User                 | 510 (32.97)           | 10,257 (31.57)             | 0.97 (0.87-1.08)                | 0.98 (0.87-1.09)                       |
| 10-year average use\(^c\) |                     |                            |                                 |                                        |
| Non-User             | 1,037 (69.32)         | 22,228 (70.45)             | 1.00 referent                   | 1.00 referent                          |
| Low                  | 201 (13.44)           | 4,381 (13.88)              | 0.99 (0.85-1.15)                | 0.97 (0.83-1.14)                       |
| High                 | 258 (17.25)           | 4,944 (15.67)              | 0.95 (0.83-1.09)                | 0.96 (0.83-1.11)                       |
| p-trend              |                       |                            | 0.45                            | 0.56                                   |
| **Ibuprofen**        |                       |                            |                                 |                                        |
| Non-User             | 1,225 (79.29)         | 25,090 (77.20)             | 1.00 referent                   | 1.00 referent                          |
| User                 | 320 (20.71)           | 7,408 (22.80)              | 1.00 (0.89-1.13)                | 0.99 (0.87-1.13)                       |
| 10-year average use\(^c\) |                     |                            |                                 |                                        |
| Non-User             | 1,225 (80.54)         | 25,090 (78.61)             | 1.00 referent                   | 1.00 referent                          |
| Low                  | 193 (12.69)           | 4,454 (13.96)              | 1.01 (0.88-1.16)                | 1.01 (0.87-1.17)                       |
| High                 | 54 (3.55)             | 1,215 (3.81)               | 1.01 (0.78-1.30)                | 1.00 (0.77-1.31)                       |
| p-trend              |                       |                            | 0.90                            | 0.94                                   |
| **Non-Aspirin NSAIDs** |                     |                              |                                 |                                        |
| Non-User             | 1,139 (75.53)         | 23,435 (73.99)             | 1.00 referent                   | 1.00 referent                          |
| User                 | 369 (24.47)           | 8,238 (26.01)              | 1.01 (0.90-1.14)                | 1.01 (0.89-1.15)                       |
| 10-year average use\(^c\) |                     |                            |                                 |                                        |
| Non-User             | 1,139 (75.53)         | 23,435 (73.99)             | 1.00 referent                   | 1.00 referent                          |
| Low                  | 282 (18.70)           | 6,474 (20.44)              | 0.99 (0.87-1.13)                | 0.99 (0.86-1.14)                       |
| High                 | 87 (5.77)             | 1,764 (5.57)               | 1.08 (0.87-1.34)                | 1.08 (0.86-1.37)                       |
| p-trend              |                       |                            | 0.68                            | 0.68                                   |

\(^a\) HR, Hazards Ratio; CI, Confidence Interval

\(^b\) Adjusted for age, race, education, body mass index, multivitamin use, PSA test in the past 2 years, benign prostate biopsy, enlarged prostate, family history of prostate cancer, diabetes, coronary artery disease, osteoarthritis, rheumatoid arthritis, chronic joint pain, chronic headaches, and migraines

\(^c\) 10-year average use: non-user; low use, <4 days/week or <4 years; high use, ≥4 days/week and ≥4 years
Table 2. Associations between NSAIDs and prostate cancer defined by grade among male VITAL participants, 2004-2007 (n=33,553).

| NSAID                  | Low-Grade Cases | High-Grade Cases | Non-Cases   | Low-Grade Multivariable-Adjusted HR (95% CI) | High-Grade Multivariable-Adjusted HR (95% CI) |
|------------------------|-----------------|------------------|-------------|--------------------------------------------|---------------------------------------------|
|                        | n = 733         | n = 213          | n = 32,582  |                                            |                                             |
|                        | N (%)           | N (%)            | N (%)       |                                            |                                             |
| Low-Dose Aspirin©      |                 |                  |             |                                            |                                             |
| Non-User               | 462 (63.81)     | 137 (64.32)      | 21,552 (66.73) | 1.00 referent                             | 1.00 referent                              |
| User                   | 262 (36.19)     | 76 (35.68)       | 10,746 (33.27) | 1.04 (0.89-1.22)                          | 0.95 (0.70-1.30)                           |
| 10-year average use©   |                 |                  |             |                                            |                                             |
| Non-User               | 462 (66.96)     | 137 (68.84)      | 21,552 (69.94) | 1.00 referent                             | 1.00 referent                              |
| Low                    | 120 (17.39)     | 28 (14.07)       | 4,831 (15.68) | 1.09 (0.88-1.34)                          | 0.90 (0.59-1.38)                           |
| High                   | 108 (15.65)     | 34 (17.09)       | 4,430 (14.38) | 1.00 (0.80-1.25)                          | 0.85 (0.56-1.31)                           |
| p-trend                |                 |                  |             |                                            | 0.82                                         |
|                       |                 |                  |             |                                            | 0.42                                         |
| Regular-Strength Aspirin|                 |                  |             |                                            |                                             |
| Non-User               | 485 (66.26)     | 154 (72.64)      | 22,228 (68.43) | 1.00 referent                             | 1.00 referent                              |
| User                   | 247 (33.74)     | 58 (27.36)       | 10,257 (31.57) | 1.04 (0.89-1.23)                          | 0.73 (0.53-1.02)                           |
| 10-year average use©   |                 |                  |             |                                            |                                             |
| Non-User               | 485 (68.21)     | 154 (75.49)      | 22,228 (70.45) | 1.00 referent                             | 1.00 referent                              |
| Low                    | 112 (15.75)     | 19 (9.31)        | 4,381 (13.88) | 1.15 (0.93-1.43)                          | 0.67 (0.41-1.10)                           |
| High                   | 114 (16.03)     | 31 (15.20)       | 4,944 (15.67) | 0.97 (0.78-1.21)                          | 0.72 (0.47-1.09)                           |
| p-trend                |                 |                  |             |                                            | 0.90                                         |
|                       |                 |                  |             |                                            | 0.06                                         |
| Ibuprofen©            |                 |                  |             |                                            |                                             |
| Non-User               | 574 (78.74)     | 168 (79.25)      | 25,090 (77.20) | 1.00 referent                             | 1.00 referent                              |
| User                   | 155 (21.26)     | 44 (20.75)       | 7,408 (22.80) | 0.97 (0.80-1.17)                          | 1.18 (0.82-1.69)                           |
| 10-year average use©   |                 |                  |             |                                            |                                             |
| Non-User               | 574 (80.39)     | 168 (81.16)      | 25,090 (78.61) | 1.00 referent                             | 1.00 referent                              |
| Low                    | 115 (16.11)     | 34 (16.43)       | 4,454 (13.96) | 1.01 (0.81-1.25)                          | 1.32 (0.89-1.95)                           |
| High                   | 25 (3.50)       | 5 (2.42)         | 1,215 (3.81)  | 0.86 (0.57-1.31)                          | 0.59 (0.22-1.61)                           |
| p-trend                |                 |                  |             |                                            | 0.65                                         |
|                       |                 |                  |             |                                            | 0.89                                         |
| Non-Aspirin NSAIDs©    |                 |                  |             |                                            |                                             |
| Non-User               | 531 (74.89)     | 157 (75.48)      | 23,435 (73.99) | 1.00 referent                             | 1.00 referent                              |
| User                   | 178 (25.11)     | 51 (24.52)       | 8,238 (26.01) | 1.01 (0.84-1.22)                          | 1.20 (0.84-1.71)                           |
| 10-year average use©   |                 |                  |             |                                            |                                             |
| Non-User               | 531 (74.89)     | 157 (75.48)      | 23,435 (73.99) | 1.00 referent                             | 1.00 referent                              |
| Low                    | 140 (19.75)     | 42 (20.19)       | 6,474 (20.44) | 1.01 (0.82-1.23)                          | 1.28 (0.88-1.86)                           |
| High                   | 38 (5.36)       | 9 (4.33)         | 1,764 (5.57)  | 1.03 (0.73-1.45)                          | 0.90 (0.43-1.88)                           |
| p-trend | 0.88 | 0.57 |

*°HR, Hazards Ratio; CI, Confidence Interval*

° Adjusted for age, race, education, body mass index, multivitamin use, PSA test in the past 2 years, benign prostate biopsy, enlarged prostate, family history of prostate cancer, diabetes, coronary artery disease, osteoarthritis, rheumatoid arthritis, chronic joint pain, chronic headaches, and migraines

° Additionally adjusted for 10-year average use of regular-strength aspirin

° 10-year average use: non-user; low use, <4 days/week or <4 years; high use, ≥4 days/week and ≥4 years
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