Prostate cancer and use of nonsteroidal anti-inflammatory drugs: systematic review and meta-analysis

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CRD summary
This meta-analysis of 12 observational studies found that aspirin reduces the risk of prostate cancer, especially advanced cancers. The effect of other non-steroidal anti-inflammatory drugs was less certain. The methods of analysis appeared appropriate, but the authors did not report methods to assess study relevance or validity. There was limited information on drug doses, which may limit clinical application of the findings.

Authors' objectives
To assess the strength and consistency of any relationship between non-steroidal anti-inflammatory drugs (NSAIDs) and prostate cancer.

Searching
The authors searched MEDLINE, PREMEDLINE, BIOSIS Previews, Cancerlit, Web of Science, the Cochrane Controlled Trials Register, proceedings of meetings of the American Association for Cancer Research (1990 to 2002), and reference lists of identified papers for studies available before January 2003. The search terms were reported. Unpublished studies were included, although apart from conference proceedings and trial registers the authors did not explicitly seek unpublished literature.

Study selection
Study designs of evaluations included in the review
The authors did not report any prior inclusion criteria relating to the study design. Prospective and retrospective observational studies were included.

Specific interventions included in the review
Studies were eligible for inclusion if they assessed the use of any single NSAID or a mixture of NSAIDs. The included studies assessed aspirin, groupings of NSAIDs other than aspirin, and groupings of both aspirin and other NSAIDs. The authors did not report the different drug names or dosages used in the included studies.

Participants included in the review
The authors did not report any prior inclusion criteria regarding the participants. Where reported, the mean age of the participants in the included studies was between 64 and 76 years. Other participant characteristics were not reported.

Outcomes assessed in the review
Studies were eligible for inclusion if they assessed the incidence of prostate cancer. In the included studies, prostate cancer was measured as the total incidence and/or as the incidence of advanced prostate cancer.

How were decisions on the relevance of primary studies made?
The authors stated that they 'independently reviewed all studies for inclusion'; this implies that more than one reviewer was involved in the selection process, though this was not stated explicitly.

Assessment of study quality
The authors did not state that they assessed validity.

Data extraction
Data were extracted using a standardised form to enhance consistency. The authors did not report how many reviewers performed the data extraction, but it appears that more than one author extracted the data independently. Any discrepancies were resolved through discussion and consensus. Publication details, method of data collection, geographic region, participant characteristics, drug type, and incidence of prostate cancer were extracted. Where available, the authors extracted covariate adjusted relative risk estimates (odds or rate ratios). When these data were not available, they were obtained from the original investigators.

**Methods of synthesis**

How were the studies combined?
The authors calculated summary odds ratios (ORs) using fixed-effect and random-effects models. To assess publication bias they used funnel plots and statistical tests (Kendall’s score, Begg’s test and Egger’s test).

How were differences between studies investigated?
The results were reported stratified by drug type and outcome (advanced prostate cancer or total incidence of prostate cancer). The authors used Cochran’s Q test to assess consistency of the summary measures. They performed subgroup analyses to assess possible sources of statistical heterogeneity between studies (including study design, outcomes examined, drug type, recruitment period, and country where the study was conducted).

**Results of the review**
The review included 12 studies (n=12,238): 5 cohort studies (n=5,416), 2 nested case-control studies (n=4,034) and 5 retrospective case control studies (n=2,788).

The authors found little evidence of publication bias from the funnel plots and statistical tests.

Aspirin was associated with a reduced risk of prostate cancer. The pooled OR for total incidence of prostate cancer was 0.85 for prospective studies (95% confidence interval, CI: 0.77, 0.94) and 1.01 for retrospective studies (95% CI: 0.86, 1.18).

The protective effect of aspirin was stronger for advanced cancers (OR 0.7, 95% CI: 0.52, 0.94; heterogeneity P=0.967) than for total incidence of prostate cancer (OR 0.9, 95% CI: 0.82, 0.99; heterogeneity P=0.317). However, the effects varied by geographic region and study design.

Studies of mixtures of different NSAIDs had less consistent findings: the odds ratio was 0.87 (95% CI: 0.61, 1.23) for non-aspirin NSAIDs (heterogeneity P=0.005) and 0.67 (95% CI: 0.37, 1.22) for mixture of aspirin and non-aspirin NSAIDs (heterogeneity P<0.001).

The authors reported further details of subgroup analyses to account for heterogeneity between the studies. There was no consistent information available about the effect of dose and duration of NSAIDs.

**Authors’ conclusions**
Taking aspirin reduces the risk of prostate cancer. The effect was stronger for advanced cancers than for total incidence of prostate cancer. The effects of other NSAIDs are less certain.

**CRD commentary**
This review included a specified research question and inclusion criteria for the outcomes and interventions of interest. However, the authors did not report in detail the specific NSAIDs included (apart from aspirin) or their dosage. As the authors noted, none of the included studies contained adequate information on the duration of drug use or time since first NSAID use. This makes it difficult to assess how the findings could be applied in clinical practice.

The search strategy appeared appropriate, although the authors acknowledged that, apart from selected meeting proceedings, they did not search for unpublished studies. It is possible that some relevant studies might have been omitted, but the authors had few exclusion criteria and no language restrictions. The authors did not describe how the
studies were assessed for validity. This made it difficult to judge the overall quality of the review and the studies on which it was based. However, the authors did describe the data extraction process and the methods used to assess publication bias and heterogeneity in some detail. This gives more confidence that the authors took steps to reduce potential sources of bias. Even so, they noted that many of the included studies were methodologically poor or had some misclassification problems, which may impact on the generalisability of the findings.

The method of analysis generally appeared appropriate. The authors’ conclusions are supported by the data presented but the lack of information on drug doses and duration, as well as the limited quality of the included studies, may make it more difficult to apply these findings in practice.

Implications of the review for practice and research
Practice: The authors did not explicitly state any implications for practice.

Research: The authors stated that there is a need for further epidemiological research to confirm the direction and magnitude of the relationship between prostate cancer and aspirin and other NSAIDs.

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